Clinical evaluation of a new optical fibre method of measuring oxygen saturation using photoplethysmograph signals reflected from internal tissues

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CLINICAL EVALUATION OF A NEW OPTICAL FIBRE METHOD OF MEASURING OXYGEN SATURATION USING PHOTOPLETHYSMOGRAPH SIGNALS REFLECTED FROM INTERNAL TISSUES

A thesis submitted for the degree of Doctor of Medicine (Research) in the University of London

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ABSTRACT

Traditional methods of measuring oxygen saturation, e.g. pulse oximetry, depend on an adequate peripheral circulation and have a 20–30 second lag time before readings are obtained. This was a series of evaluations of novel optical probes, designed to measure oxygen saturation using fibreoptic technology directly from internal organs including the brain, oesophagus and organs with splanchnic circulations. A series of pilot studies were proposed and research ethics approval obtained to carry out studies in humans, under general anaesthesia, using these probes. Innovative reflectance probes were designed specifically for each of the four applications, so as to obtain potentially useful signals needed for signal processing, analysis and evaluation.

Signals were successfully obtained from the brain, oesophagus and splanchnic region in almost all of the patients recruited. Good quality photoplethysmograph signals were recorded and these were translated into clinically meaningful values of oxygen saturation comparable to traditional methods of pulse oximetry. Overall, the signals were prone to movement artefacts as well as occasional interference from surgical diathermy and other sources. Nonetheless, the probes could prove to be a useful alternative to conventional external transmittance pulse oximetry methods as well as providing useful information regarding regional perfusion and oxygenation. The success of these pilot studies will form the basis of more research in the area and further development of such probes on the medical engineering front.

CONTENTS

LIST OF FIGURES AND TABLES

LIST OF ABBREVIATIONS

BP	Blood pressure
CBF	Cerebral blood flow
CBV	Cerebral blood volume
CPP	Cerebral perfusion pressure – the difference between the mean arterial pressure and the intracranial pressure
CSF	Cerebrospinal fluid
CT	Computerised tomography
CVP	Central venous pressure
ECG	Electrocardiogram
$EtCO_2$	End-tidal carbon dioxide concentration
FDG	Flurodeoxyglucose – contrast used in PET scans
GCS	Glasgow Coma Scale
Hb	Haemoglobin
ICP	Intracranial pressure
LED	Light emitting diode: semi-conductor light source
MAP	Mean arterial pressure
MRI	Magnetic resonance imaging
NA	Numerical aperture
NIRS	Near-infrared spectroscopy
$PbtO_2$	Brain oxygen tissue tension
PCO_2, PO_2	Partial pressures of carbon dioxide and oxygen respectively
PET	Positron emission tomography
PPG	Photoplethysmograph
SaO_2	Arterial oxygen saturation measured using a haemoximeter
ScO_2	Cerebral oxygen saturation estimated by near-infrared spectroscopy

$SfcO_2$	Oxygen saturation estimated from the cardiac frequency component of a fast Fourier transform
$SfrO_2$	Oxygen saturation estimated from the respiratory frequency component of a fast Fourier transform
$SjvO_2$	Jugular venous bulb oxygen saturation
SmO_2	'Mixed' oxygen saturation – the oxygen saturation of blood within tissue, estimated from the total intensity of backscattered light. Measurements from arterial, venous and capillary blood components
SpO_2	Arterial oxygen saturation estimated using a pulse oximeter
VI	Virtual instrument

CHAPTER ONE – INTRODUCTION

As an anaesthetist, I am at the forefront of the usage of modern monitoring equipment for looking after the unconscious patient. Whether deliberate or not, as anaesthetists and clinicians, we are often presented with the opportunity to use the latest given technology to aid us in looking after our patients. This encompasses anything from the newest anaesthetic machines or ventilators available, to syringe pumps for titrating medications, or fibreoptic endoscopes for performing laryngeal intubations in patients with difficult airway anatomy. There are several questions which spring to mind when thinking about existing technology: namely, how we can improve what we already have; and the role of future devices developed in anaesthesia and surgery that could make a difference to clinical care.

Oxygenation, and the ability to measure oxygen levels in the human body, accurately, speedily and with nil or minimal side effects, is key in many areas of medicine and surgery. It is assumed that well oxygenated tissue goes hand in hand with healthy viable organs as opposed to tissue that has been starved of oxygen. There are devices in the market already that measure global oxygenation in the body (pulse oximetry, CO-oximetry) but none really to measure specific end-organ oxygenation. Those devices in existence such as pulse oximetry, have changed medicine and surgery tremendously in the past twenty years, but also have their limitations (which will be discussed in detail in chapter two). In addition, global oxygenation does not necessarily indicate adequate regional oxygen supply and/or adequate perfusion of end organs in times of stress or illness.

There is a clinical need, unmet by current commercially available technology, for measuring end-organ perfusion in the brain, kidney, bowel, when these structures are damaged in disease or trauma. For example, in patients who have sustained a head injury, and have intracranial monitoring in situ, a sustained rise in intracranial pressure (ICP) is a global indicator that things are not normal. If more information such as brain oxygen saturation could be obtained at the same time, it could influence the speed as well as strategy for intervention on that patient.

In order to make these ideas a reality, expertise was needed from engineers at City University with a research background in biomedical optics. In collaboration with this group, the challenge was to develop a set of devices that could have a distinct role to play in enhancing the current equipment we already have and/or to fulfil an area of unmet need using optics in the clinical setting.

Probes and instrumentation were developed, capable of measuring tissue oxygenation in areas where traditional methods are not completely accurate, as well as in areas where this had not been done before. One of the main aims was to develop a device that could overcome some of the limitations shown in readily used monitoring equipment (e.g. pulse oximetry). Thus, much of the methodology involved comparison with traditional monitoring methods and the protocol for each study was written specifically with this in mind.

Most physiological measurements are made using sensors, which measure a physical quantity (measurand) and converting it into a clinically useful variable using an appropriate algorithm. In this research the principal measurands were photoplethysmographic signals, from which oxygenation and perfusion may be derived. Three distinct and novel monitoring sites were chosen, all of which are at risk of compromised perfusion in critically ill patients: the brain, the oesophagus and the abdominal organs. All three sites are difficult to access, so optical fibre sensors were a prerequisite for transmitting light to and from the tissue.

The proposed research projects were a series of clinical evaluations of new optical methods of monitoring the oxygenation of blood within tissue, to achieve the above aims. Fibreoptic probes were developed specifically for measurement from tissue sites within the body. Using essentially the same technology platform for different applications, probes were developed that allowed measurement of oxygen saturation in three different areas of the human body.

The thesis is comprised of three main parts: measurement of oxygen saturation within brain tissue via a cranial bolt, measurement of oxygen saturation within the oesophagus, and finally measurement within the abdominal cavity. The measurement of oxygen saturation within the brain occurred in patients undergoing elective

neurosurgery, as well as in the patient with intracranial pathology. Measurements taken from the oesophagus and abdominal cavities were from that of anaesthetised patients undergoing elective surgery.

As with any research project undertaken, full peer review, ethical approval along with medical physics testing and Medicines and Healthcare products Regulatory Agency (MHRA) were needed before the research was carried out in patients. I was the key investigator involved with preparing the protocol, idea development and design, along with obtaining full ethics approval. I was one of the main clinical recruiters of patients for the studies; and was the main liaison between the research and surgical teams whose patients we recruited for the studies.

As a prelude to the three main studies–with pulse oximetry the common theme and impetus for this research–I will describe the history and evolution of pulse oximeters in chapter two. The development of an innovative fibreoptic probe and the research that followed was to negate some of the limitations of classic pulse oximetry. In chapter three, I will describe the current management and monitoring of patients with intracranial pathology, the problems with current treatment and diagnosis, and the application of a new fibreoptic probe in research for monitoring oxygen saturation in patients with intracranial pathology. The chapters after that will contain the descriptions and findings of using this fibreoptic technology, in obtaining oxygen saturation readings from the oesophagus, and also from the abdominal cavity.

CHAPTER TWO – PULSE OXIMETRY

2.1 Background and evolvement of pulse oximetry

The balance between oxygen delivery and consumption in all human beings is the essence of survival. Though some organs in the body can rely on anaerobic metabolism to survive for a short period of time, others such as the brain or heart require a constant supply of oxygen for aerobic metabolism and are most sensitive to change, with a high risk of damage should the demand for oxygen exceed supply. (1)

Oxygen is vital to the functioning of every cell in the human body. In the absence of oxygen for a prolonged period, cells will die. Pulse oximetry was developed in 1971 by Aoyagi using the ratio of red to infrared light absorption of pulsating components at the measuring site.(2)(3) Pulse oximetry differentiates between the pulsatile component that is arterial blood and the venous capillary blood (smooth flowing). It was commercialised in 1981 by BIOX/Ohmeda and in 1983 by Nellcor. Pulse oximetry was introduced into clinical practice in the United States of America when it was first brought into the operating department as a simple, non-invasive way of continuously being able to measure patients' oxygen saturation. The introduction of commercially available pulse oximeters revolutionised the practice of anaesthesia and patient monitoring in healthcare settings across the world. In the United Kingdom as in many other countries, pulse oximetry is mandatory monitoring during every general anaesthetic. (4)

Pulse oximetry is not only able to provide real-time monitoring of a patient's oxygen saturation but is able give a continuous reading of heart rate. Over the years, the recognised advantages of this user friendly, relatively low cost device has given it an established niche in clinical practice. The probe is usually applied to the finger, but has been applied to other areas such as the ear and nose. There are, however limitations to the use of pulse oximetry. Pulse oximetry is a measure of oxygenation only and not of ventilation. It gives no measure of carbon dioxide levels, blood electrolytes or blood pH. Pulse oximetry may also be inaccurate or fail in cases of hypoperfusion, peripheral vasoconstriction or motion artefacts. It can also be inaccurate in the presence highly calloused skin, low signal-to-noise ratio, abnormal

pulse rates, irregular rhythm, ventilator-induced and venous pulse interference, ambient light, electrosurgery, skin pigments/dyes/nail polish, burns and dysfunctional haemoglobins. As oximetry is simply based on colorimetric or spectrophotometric methods; a simple system (dual wavelengths) is unable to identify the presence of abnormal haemoglobins, and hence carboxyhaemoglobin (found in heavy smokers or in carbon monoxide poisoning from combustion products) which is cherry red will result in a falsely high reading, although the actual percentage of oxyhaemoglobin may be critically low. The presence of methaemoglobinaemia characteristically causes pulse oximeters to under read around 85% saturation. Whilst pulse oximeters give an indication of the adequacy of oxygenation of arterial blood, it is not an indicator of organ tissue oxygenation and overall well-being.(5)

2.2 How pulse oximeters work

2.2.1 Photoplethysmography

The photoplethysmograph (PPG) trace is derived from the change of attenuation of light energy transmitted or reflected through the tissues over which the pulse oximeter has been applied. (6) When the probe is attached to the fingertip or the earlobe, the pulsations detected are almost exclusively from the cutaneous vascular bed. Any factors that regulate blood flow of the skin will have a profound effect on the plethysmogram. The following are some factors that affect cutaneous blood flow:

- Neurogenic factors: sympathetic vasoconstrictor fibres, cholinergic innervations to sweat glands resulting in vasodilation
- Reflex vasoconstriction in skin: local /central cooling, hypotension, painful stimuli, fear, deep inspiration
- Reflex vasodilatation in skin: heating, stimulation of chemoreceptors, coronary occlusion, acute hypertension
- Humoral control: α-adrenergic, serotonin, prostaglandins, vasopressin, angiotensin, all causing vasoconstriction
- Miscellaneous: systemic hypoxaemia/hypercapnia

Most commercially available pulse oximeters feature a display of the real-time photoplethysmograph signal. The photoplethysmograph obtained by a pulse oximeter is obtained by shining light through the tissue and essentially measuring changes in the amount of light absorbed by the tissue. In addition, it is feasible to obtain a (reflectance) photoplethysmograph from light "reflected " (actually re-emitted) by the tissue.

2.3 Physical/optical principles

Pulse oximetry is based on the Beer-Lambert law which states that for a beam of monochromatic radiation passing through a homogeneous solution, the absorbance is proportional to the product of the concentration and path length. A source of light originates from the probe at two wavelengths (650 nm and 805 nm). The light is partly absorbed by haemoglobin, by amounts which differ depending on whether it is saturated or desaturated with oxygen. By calculating the absorption at the two wavelengths the processor can compute the proportion of haemoglobin which is oxygenated.

Commercial devices show a displayed trace on screen – composite of filtered signals giving a smoothed shape and amplitude trend of PPG to give an oxygen saturation reading. The concentration of an apparently transparent substance in solution may be measured spectrophotometrically. In a spectrophotometer, radiant energy is shone through a cuvette of known path length containing the substance being analysed. The energy source is usually a wide-bandwidth incandescent lamp, with a monochromator (e.g. prism, diffraction grating, or interference filters) in place to produce a single wavelength beam of energy. A proportion of the energy is absorbed by the solution under analysis. The Beer-Lambert law relates the fraction of radiant energy absorbed by the substance to the concentration and amount of the substance by the following formula:

$$A = \log(I_0/I) = \varepsilon l c \qquad (2.1)$$

Where A is the absorbance of the sample and is proportional to the concentration (c) and the path length (l); and ε is the molar extinction coefficient in Equation (2.1),

which is a wavelength dependent constant characterising the sample. It is defined as the optical density of an absorbing substance in a concentration of 1 mmol/l measured with a light path length of 1 cm at a specific wavelength. I_0 is the intensity of the energy without the sample, and I is the intensity with the sample.

Oximetry by any spectrophotometric means relies on the change in absorption of electromagnetic energy with change in the percentage of oxygen bound to haemoglobin (Hb). Human haemoglobin has a molecular weight of around 64585 Daltons and contains two pairs of polypeptide chains: the α- chains and the β-chains. Each polypeptide chain is combined with one haem group which has one atom of iron in the ferrous state and is able to bind reversibly with one molecule of oxygen. The quaternary structure of the four chains is of critical importance to pulse oximetry as the change in the shape of this quaternary structure with the degree of oxygenation alters the optical absorption spectrum proportionately and forms the basis of optical absorption oximetry. Figure 2.1 shows the absorption spectra of haemoglobin.

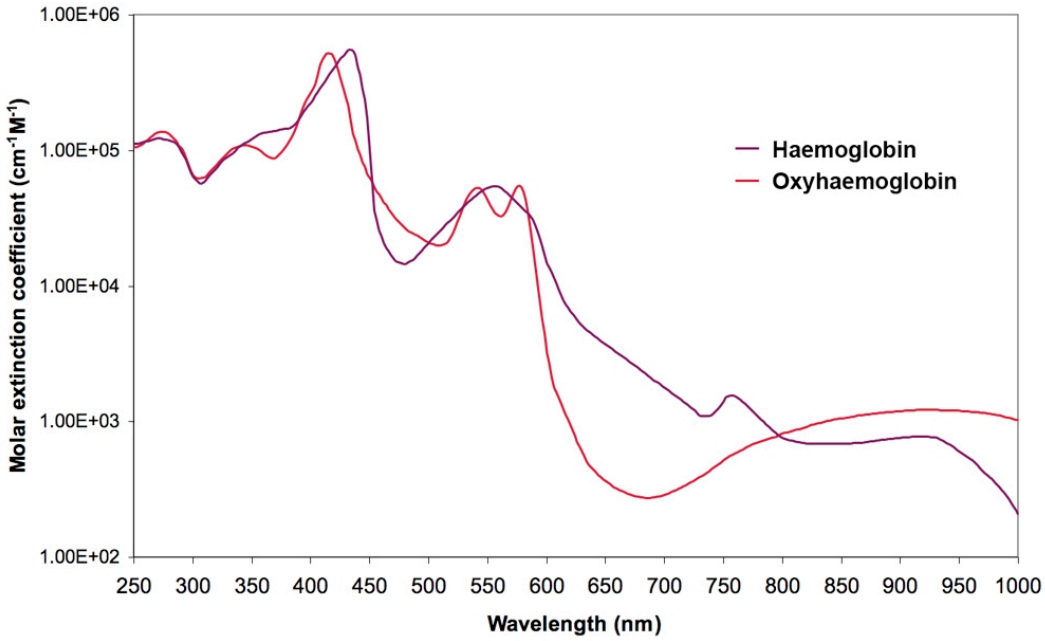


Figure 2.1 Absorption spectra of oxygenated and deoxygenated haemoglobin in the near-ultraviolet to near-infrared range. Data from (7); Image reproduced from(8).

The pulse oximeter is dependant on a pulsatile flow and produces a graph of the quality of flow. Where flow is sluggish (e.g. hypovolaemia or vasoconstriction) the pulse oximeter may be unable to function. The computer within the oximeter is capable of distinguishing pulsatile flow from other more static signals (such as tissue or venous signals) to display only the arterial flow. Nearly all currently available conventional pulse oximeters make use of two wavelengths of light, usually 660 nm and 940 nm. The light is generated in the probe by a combination of light-emitting diodes with a miniature semiconductor photodetector, which is enclosed into a compact probe for attachment to the fingertip or earlobe. The probe is connected to the main unit via a small lightweight cable. The exception to this setup are the probes used in magnetic resonance imaging (MRI) scanner where all of the electronic components are in the main unit, and the light energy is transmitted to and from the patient by optical fibres.

Conventional pulse oximeters function by comparing the absorption of energy at two wavelengths, usually 660 nm and 940 nm. A value, SpO_2, is approximately equal to arterial haemoglobin saturation, SaO_2, which is determined from the ratio of the absorption of the energy at the two wavelengths, by the pulsating blood component of the tissue (i.e. the arterial blood). The range of wavelengths over which spectrophotometric techniques can be used *in vivo* is limited to the range between 600 and 1300 nm. At wavelengths less than 600 nm, melanin in skin causes a high level of absorption and at longer wavelengths of above 1300 nm, there is a stronger absorption due to the water content in the tissues. At the isobestic points, where the two lines cross each other on the graph, are the wavelengths at which the ε values of the two–oxygenated and deoxygenated haemoglobin are equal. The isobestic points can be used in combination with another wavelength with a large difference in absorption to correct for changes in intensity caused by factors such as probe placement.

The light emitting diodes are placed in close contact with the skin surface. The light energy is detected with a semiconductor detector, placed on the skin perpendicularly opposite the diodes in the case of the transmittance pulse oximeters. A few pulse oximeters have the detector mounted adjacent to the light emitting diodes. In practice, the light absorption through the finger varies by about 1–2% of the total

absorption, partly due to haemoglobin content and path length changes in the cardiac cycle i.e. with the pulsatile expansion of the finger with each bolus of blood. The alignment of the erythrocytes also changes during different periods of the cardiac cycle, which contribute to the changes in absorption.

The pulse oximeter is able to measure changes in absorption of light energy by oxy and deoxy-haemoglobin and is able to indicate the percent of haemoglobin which is oxygen saturated. Pulse oximeters perform spectrophotometry either by reflection from the skin or by transmission through an extremity; it is the latter that is the most commonly used method. The extremity e.g. the finger, needs to have a reasonably short optical path length to be sufficiently translucent at the wavelengths used, which are in the region of 600 nm to 1300 nm. Conventional pulse oximetry requires the use of one wavelength each side of the 805 nm isobestic point on the absorption spectra of adult haemoglobin. The Beer-Lambert law applies only for monochromatic radiation through a homogenous isotropic medium (one in which the refractive index is the same in all directions) with negligible scattering, where there is no association or dissociation of absorbing molecules. Light emitting diodes (LEDs), although strictly not monochromatic, can be used as a suitable energy source. With separate energy sources for each wavelength negating the need for narrow-bandwidth interference filters. LEDS can also be switched on and off very rapidly, as they do not have the thermal inertia of incandescent energy sources. Thus making it possible to use a single photodetector if the LEDs are used in this manner.

A single photodetector is used to detect the energy alternately from both LEDs. In conventional transmission pulse oximetry, this is positioned perpendicularly opposite to the LEDs with the extremity held tightly between them. The flexible cable from the probe to the pulse oximeter unit carries the power to the LEDs and the signal from the photodetector. The main unit of the pulse oximeter contains electronic circuitry with functions listed below:

- Amplification of the photodetector signal
- Separation of the red and infrared plethysmograph signals
- Switching and control of current through LEDs

- Adjustment of the gain of one of the two signals to make them equivalent
- Analogue-to-digital conversion of the red and infrared signals
- Reduction or elimination of artefacts
- Calculation of the oxygen saturation (SpO_2)
- Display consisting of SpO_2, plethysmogram and heart rate
- Control of alarms
- Storage of SpO_2 trends

2.4 Calibration of pulse oximeters

The first pulse oximeters were calibrated based on the Beer-Lambert Law which applies only under conditions of non-turbidity, a single unknown solute and a fixed optical path length. Thus, empirical data is used for calibration instead. Until recently, calibration occurred *in vivo* by comparison with samples of arterial blood analysed with a haemoximeter, a laboratory instrument also known as a CO-oximeter. Small samples of heparinised blood are haemolysed and passed into a transparent (often quartz) cuvette of fixed and known path length. This gives highly accurate readings of oxygen saturation at the time the blood is taken. It measures this using the principle of spectrophotometry, but using many more wavelengths of light than the two used in pulse oximetry. A wideband light source e.g. tungsten halogen lamp, is directed through the cuvette and the transmitted light passes through a monochromator which separates the light into its component wavelengths.

Modern instruments measure the transmitted intensity of up to 128 separate wavelengths over a range of 500 nm to 700 nm using an array of photodiodes amplified, converted from a digital to analogue signal, and passed to a microprocessor, which calculates the oxygen saturation using numerical solutions to simultaneous equations based on selected wavelength measurements. The haemoximeter is also able to calculate the following values directly: oxy-haemoglobin, carboxyhaemoglobin, methaemoglobin, “free haemoglobin”, sulph-haemoglobin; and the following derived readings: total haemoglobin, fractional oxygen saturation, functional oxygen, oxygen capacity and oxygen content.

Since the blood is haemolysed, an effective haemoglobin solution is produced, so the Beer-Lambert law can be applied directly producing greater accuracy than *in vivo* methods. This is in contrast to pulse oximeters which must compensate for scattering effects within the tissue. They are instead calibrated by the manufacturers using empirical data from volunteer studies as follows: probes were placed on the volunteers' fingers, with them initially breathing air with enough oxygen to raise the arterial saturation to 100%. They then breathed an atmosphere of progressively less oxygen with proportionately more nitrogen. The atmosphere is made progressively more hypoxic in stages, each time allowing the volunteer to equilibrate at each new level of arterial saturation. When the pulse oximeter reads a steady saturation, samples of arterial blood are taken and tested in a CO-oximeter. A calibration curve of SpO_2 versus SaO_2 (true arterial oxygen saturation) can be plotted. There are obvious limitations to the level of oxygen desaturation ethically permissible in the healthy volunteer subjects, who desaturate by breathing progressively more hypoxic mixtures, due to the risk of hypoxic brain damage and/or injury associated with loss of consciousness. Also, because of this limitation, any values of SpO_2 below 70% are extrapolated and thus not accurate. In addition, the position of the calibration points all closely spaced on the curve, leads to further inaccuracy in plotting.

The development of an *in vitro* testing that can enhance accuracy and avoid the pitfalls of *in vivo* testing was necessary. Many devices, from the very simple to more complex have been developed to simulate artificial haemoglobin solutions and absorption. The advantages of *in vitro* calibration are the following:

- Data points on the curve can be extended below 70%
- Calibration studies are able to be repeated more readily
- Safe in terms of subject's morbidity
- Effects of abnormal haemoglobins may be assessed easily
- Standardisation of calibration
- Effects of both physical and chemical interfering agents could be tested in a standardised fashion
- Repeated calibration checks against the standard is possible

2.5 Medical applications and limitations of pulse oximetry

Pulse oximetry provides an empirical measure of arterial saturation. It has become one of the minimal standards of monitoring in anaesthesia, critical care and in the post-operative recovery period. Pulse oximetry has probably been one of the greatest advances in patient monitoring in the past two decades. The ease of use, and ability to continuously monitor oxygen saturation by the bedside, in a non-invasive manner, has made it an acceptable, standard of monitoring in anaesthesia, in the post-operative recovery room, on the critical care unit and on most medical wards. Due to its portable nature, it can also be found and used in ambulances and medical vehicles in the United Kingdom.

The ability for pulse oximetry to detect changes in oxygen saturation has indeed cemented its place in routine clinical monitoring in anaesthesia and critical care, with beneficial outcome for patients and staff alike. A closed claim analysis concluded that the incidence of critical incidents due to airway accidents declined in the 1980s since the introduction of pulse oximetry.(9) This led to the American Society of Anaesthesiologists declaration of pulse oximetry to be one of the minimal standards of monitoring in anaesthesia in 1990. (10)

The general correlation between SpO_2 obtained by conventional pulse oximetry and actual arterial blood oxygen saturation is reasonably accurate–usually a less than 3 % discrepancy in readings provided the arterial oxygen saturation is above 70%. Whilst pulse oximetry is accepted as a non-invasive monitoring device that can fairly accurately detect hypoxemia in surgery, critical and anaesthesia; in cases where accuracy is paramount, such as detecting hyperoxia, the use of pulse oximetry is not so clear. (11)

Critical incidents due to pulse oximeter errors are rare. The person using it must bear in mind its limitations and potentials for failure during its calibration period and application in clinical use. Oximeters are calibrated during manufacture and their internal circuits automatically checked when they are turned on. They are accurate in the range of oxygen saturations of 80 to 100% (±2%), but less accurate under 80%. The pitch of the audible pulse signal falls with reducing values of saturation. (12)(13)

The size of the pulse waveform is displayed graphically. In the clinical setting, the alarms on the machine 'go off' in response to changes in pulse rate beyond the set levels or oxygen saturation readings below 90%. This point suggests a marked deterioration of levels of oxygen in the blood, which could lead to serious problems if not rectified. While the response time of the pulse oximeter is generally fast, there can be quite a significant delay between a drop in arterial oxygen tension and a change in reading by the pulse oximeter. Delay in response is related to sensor location, with a quicker response when the sensor is placed more centrally. Factors affecting this delay or 'lag time' is influenced by poor peripheral perfusion due to hypothermia, peripheral vasoconstriction and motion artefacts. Drugs which can cause vasoconstriction such as adrenaline or vasospastic conditions such as Raynaud's Syndrome can lead to a poor trace. Increasing the time over which the pulse signals are averaged can also increase the lag time.

Figure 2.2 shows the oxygen dissociation curve, which illustrates the way in which oxygen is released to body tissues. The sigmoid shape of the curve shows how oxygen saturation is related to partial pressure of oxygen in the body. Haemoglobin's affinity for oxygen increases the more molecules of oxygen bind to it. At pressures above 70 mmHg, the curve is rather flat, implying that the oxygen content of blood does not alter much despite large increases in oxygen partial pressure. The P50 also known as the partial pressure of oxygen in blood at which haemoglobin is 50% saturated, is around 26 mmHg, i.e. a measure of how much affinity haemoglobin has for oxygen. Disease, or other factors such as acidosis, or an increase in temperature or the presence of 2-3 DPG (diphosphoglyceric acid), shifts the curve to the right and hence changes the affinity of oxygen for haemoglobin. This is in order to allow the body more oxygen as required. Focusing on the steep part of the oxygen dissociation curve, the correlation between values obtained from SpO_2 and actual oxygen content of blood is not linear, and any values below 90% is unreliable and must be considered to be a clinically meaningful change unless known otherwise.

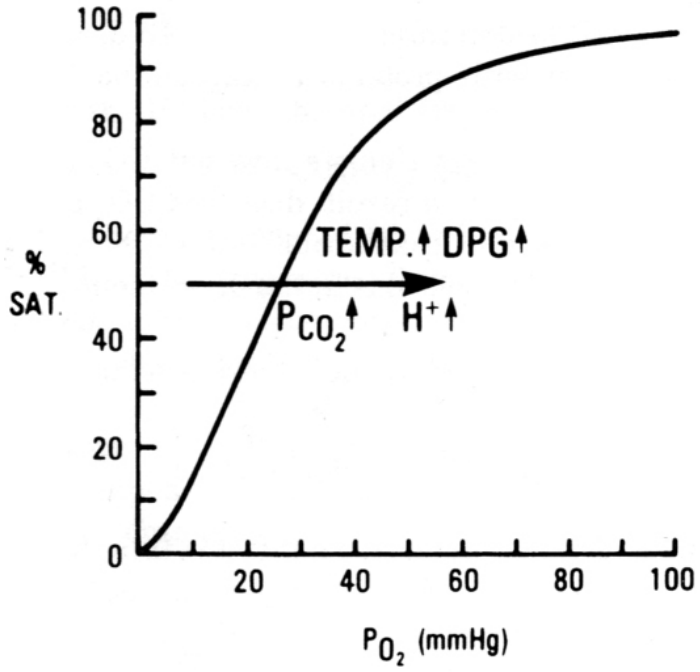


Figure 2.2 Oxygen dissociation curve. Adapted from (14).

Other reasons for unreliable readings include bright overhead lights in theatre; the signal may also be interrupted by surgical diathermy;(15) shivering may cause difficulties in picking up an adequate signal.(16) When methylene blue is used in surgery to the parathyroids or to treat methaemoglobinaemia, a short-lived reduction in saturation estimations is registered. (17) Nail varnish may cause falsely low readings. However the readings are not affected by jaundice, dark skin or anaemia.(18)(19)(20)

Pulse oximeters from different manufacturers can also give different readings.(21) One reason for this is the differences used in calibration methods between different pulse oximeters and the variations in time it takes different monitors to detect a change in saturation. The manufacturing differences and errors in calibration or even the time over which the signals are averaged in a pulse oximeter, can lead to delays and problems during critical junctions of time when looking after a patient. It is therefore of utmost importance for the individual using this technology to be aware of the specifications and limitations of the equipment used in order to avoid any potential pitfalls. (22) In addition to its use in theatres and critical care areas, pulse oximetry is also used on wards for intermittent monitoring during routine bedside

observations, as well as in the transport of patients around the hospital, in the back of ambulances, and in medical clinics in the community due to its ease of use and portability.

In recognition of the importance of the use of pulse oximetry in anaesthesia, the 2010 standards for a safe practice of anaesthesia considers the use of pulse oximetry mandatory. The Association of Anaesthetists of Great Britain and Ireland (AAGBI) have taken a lead role in launching project LIFEBOX – saving lives through safer surgery; promoting and making pulse oximetry affordable and available to low-resource countries, in order to make anaesthesia and surgery safer. (23) There is no doubt that judicious use of the pulse oximeter is of enormous benefit in terms of the early detection of hypoxia and will remain the minimal standard for monitoring under anaesthesia for years to come.

2.6 New developments

There are also now commercially available devices such as the Masimo Rainbow-SET range of pulse oximeters that allow non-invasive measurement of haemoglobin concentration as well as the proportion of other haemoglobins such as methaemoglobin and carboxyhaemoglobin. (17)(22) The Masimo instruments give continuous readings of oxyhaemoglobin levels as well as oxygen saturation readings, oxygen content, and other haemoglobins, using multiple wavelengths of light. This allows the clinician additional information on oxygenation status in the patient. (24) A patient can appear well oxygenated, but still be hypoxic in the presence of carbon monoxide, as this binds to haemoglobin more avidly than oxygen does. Such a monitor, would allow us to be able to differentiate between such states. The other big advantage is that it allows bedside readings of other haemoglobins without the need for invasive and repeated blood sampling with quick results. (25) As these devices develop and increase in accuracy, there is likely to be an increase in consumer demand.

The downside of any of these older as well as newer devices, is that while it may give an indication of oxygen saturation at any given time, it does not indicate how well a patient may be ventilating (i.e. carbon dioxide exchange) nor will it indicate a

problem when used intermittently in patients who are rousable when readings are taken, but could have a problem when left alone without continuous monitoring. For example patients who have been given a dose of opioids or have sleep apnoea.

Increasingly robust and reliable technology, has allowed more avenues for the application and research into the use of photoplethysmography (PPG) waveforms.(26) A greater study into the use of the PPG waveform remains, and with it the potential for its development into multimodal monitoring systems with the ability to measure and process more than one clinical variable at once.(27) This led to the development of what was essentially a fibreoptic probe; able to make use of PPG waveforms to obtain what we believe could be clinically useful results in a clinical setting. The next section describes the idea development and process making of this probe in detail.

2.7 Development of fibreoptic probe

Optical fibres are transparent rods of glass or plastic stretched so they are thin, long and flexible.(28)The instrumentation, developed jointly by the Pain and Anaesthesia Research Centre (Barts Health NHS Trust/QMUL) and the Department of Biomedical Engineering, City University London, utilises optical fibres to transmit light to, and receive reflected and re-emitted light from the tissue.

The light-conducting principles behind optical fibres were first demonstrated in Victorian times, although modern optical fibres were only developed in the early 1950s. Optical fibres became practical for use in communications in the late 1970s, once the attenuation was reduced sufficiently; since then, several technical advances have been made to improve the attenuation and dispersion properties of optical fibres, allowing signals to travel further and carry more information.

Optical fibres have several uses in practice. They were first used in telecommunications because of the flexible properties, and that it could bundled together and travel over long distances. Fibres can be made of glass or plastic or a combination of the two. The extension of its use into medicine is due to the fact that optical fibres can be developed into sensors, capable of measuring many

physiological parameters. Variables such as temperature, blood flow, and oxygen levels can be detected and measured using optical sensors. It has also been incorporated in the use of surgical lasers, endoscopes and light sources for medical devices. The principle of operation is based on its cylindrical dielectric waveguide that allows the transmission of light along its axis, by the process of total internal reflection. The fibre consists of a core, surrounded by a cladding layer. To confine the optical signal in the core, the refractive index of the core must be greater than that of the cladding.

An optical fibre can be operated in a great variety of physical configurations. Fibreoptics are involved in the transmission of light to and from the instrument and sensor. It is the use of light in the measurement that distinguishes fibreoptics from electrical sensors. (29) An optical fibre is usually made of glass or plastic. When glass is used for an optical fibre, it is unbelievably clear. It is designed to guide light along its length by confining as much light as possible in a propagating form. The glass fibre is capable of carrying light over varying distances. It does this by converting an input signal into short flashes of light, which travel down the fibre, and at the far end, are converted to an electrical signal by means of a photoelectric cell.

The fibre is covered with a layer of glass (cladding) to avoid problems with contamination due to grease, dirt etc. The core and the cladding form a single solid fibre of glass. The optical fibre is very thin, usually a typical core size of 50 micrometres. Unlike other forms of glass, the fibre is thin and flexible and can bend easily without shattering.

Traditional methods of measuring oxygen saturation e.g. pulse oximetry depend on there being an adequate peripheral circulation and have a 20–30 second lag time before readings are obtained. With traditional pulse oximetry, values are measured around 600 times per second, an algorithm compares the measure values with stored values, then displays an averaged value over the previous five seconds. The design and build of the fibreoptic system in theory should not have this problem, and may give comparable results to traditional methods of oxygen saturation measurements.(4) It may also have the advantage of taking measurements from more central sites, thus negating the delay in taking measurements from the periphery.

The Biomedical Engineering Research Group based at City University, London, in collaboration with the Pain and Anaesthesia Research Centre at Barts Health NHS Trust, developed a system based on pulse oximeter technology, whereby oxygen saturation is measured by detecting photoplethysmographic (PPG) signals reflected from the tissues.(30) This system was built on the well-established principle of oximetry, a technique where light is used to determine the oxygen content of red blood cells by measuring the relative absorption of two wavelengths of light by haemoglobin in cells. Unlike current commercially available oximeters, which utilise external sensors, transmitting light through skin, bone and other tissue, the optical fibre system provides a means of directly accessing brain or oesophageal tissue etc. The system was built in an attempt to obtain rapid accurate regional measurement of organ tissue oxygen content. In our studies, the raw signal data was displayed on the screen automatically. All analysis was performed offline using a 10-second rolling window to calculate the SpO_2 values etc.

To date, non-invasive solutions have not succeeded fully in measuring tissue oxygen saturation. Our group has concentrated on developing probes that can be inserted into organs such as the brain and gullet. (31)(32)(33)The focus of this thesis will be the rationale for monitoring these organs, evaluation of tailor-made probes, and their potential application in clinical practice.

CHAPTER THREE – OXYGEN SATURATION MEASUREMENTS FROM BRAIN TISSUE IN NEUROSURGICAL AND INTENSIVE CARE PATIENTS

3.1 Introduction and background

Head injuries are a common cause of morbidity and mortality in trauma victims. Severe head injury accounts for more than 50% of trauma related deaths, most of which occur after road traffic accidents, falls and assaults.(34) Head injuries can be classified according to the degree of severity based upon the Glasgow Coma Scale (GCS) shown in Table 3.1. The Glasgow Coma Scale is a scale for measuring level of consciousness in which scoring is determined by three factors: amount of eye opening, verbal and motor responsiveness. It is a rough guide to predicting the duration and outcome of patients in a coma, primarily after suffering a head injury. The scale has a high degree of consistency, even when used by staff of varied experience. A GCS of less than 8 would suggest a deep or low level of unconsciousness whereas a score of 14 to15 would be the expected score in the alert, awake patient.

3.2 Pathophysiology of head injury

		Score
Eye opening	spontaneously	4
	to speech	3
	to pain	2
	none	1
Verbal response	orientated	5
	confused	4
	inappropriate	3
	incomprehensible	2
	none	1
Motor response	obeys commands	6
	localises to pain	5
	withdraws from pain	4
	flexion to pain	3
	extension to pain	2
	none	1
Maximum score		15

Table 3.1 Glasgow Coma Scale.

Primary brain injury results from the original insult, which occurred at the time of the injury. This unfortunately cannot be influenced by treatment. Injury at the time is due to deceleration forces of the brain within the skull, or lacerations from bony points inside the skull, shearing and rotational effects, and damage to blood vessels. These can be anything from intracranial haematomas (extradural, subdural or intracerebral) to diffuse axonal injury. Secondary brain injury occurs when cerebral oedema, ischaemia, infection or herniation exacerbates the original insult. Some of these can be prevented by correcting hypoxaemia, hypotension, hypercarbia, and by attention to other associated injuries.(35)(36) These secondary insults can cause permanent neurological damage and worsen outcome if left undetected and untreated.(37)

3.3 Management of head injury

The primary aim, after assessment of a trauma patient as stated in the standard Advanced Trauma Life Support (ATLS) protocol, is the prevention of the development of secondary brain injury. (38) This is done by optimising oxygenation of the patient and brain tissue perfusion. In particular, the normal autoregulation of cerebral blood flow may well be lost in a head injury, rendering the injured brain more susceptible to swings in blood pressure and hypoxia. (39)(40) Figure 3.1 illustrates how cerebral blood flow is autoregulated. As blood pressure increases, cerebral blood flow is maintained at a constant until a critical point beyond which the brain will develop ischaemia and be prone to damage. (41)

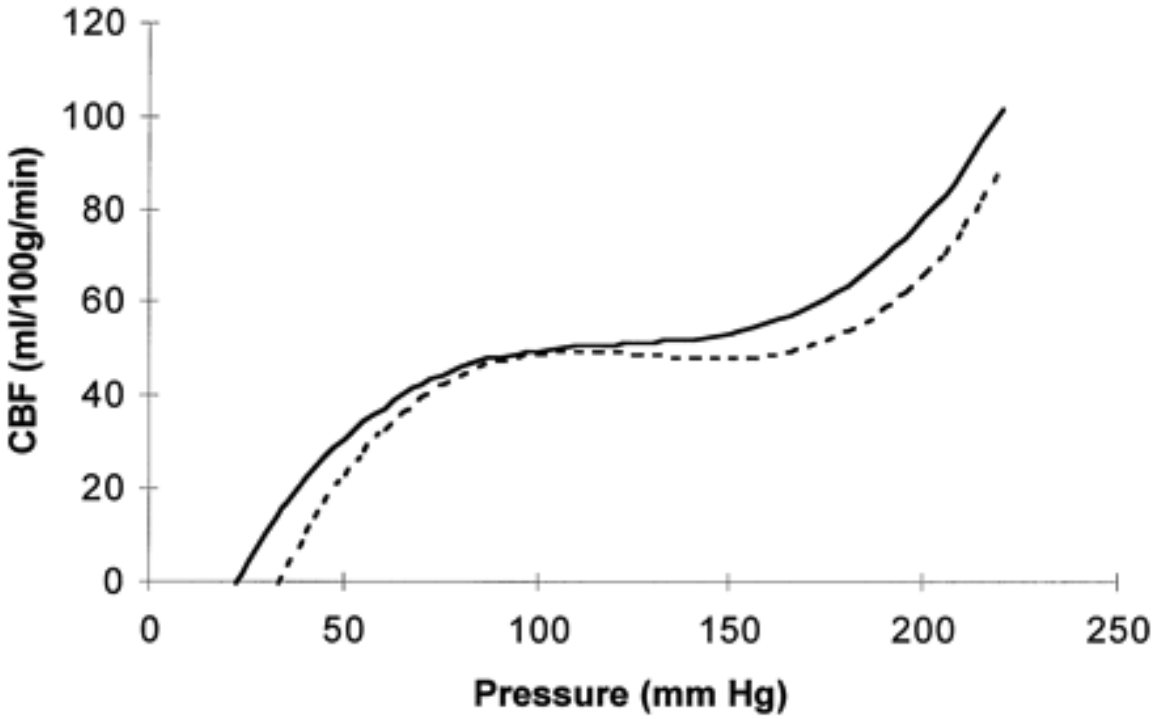


Figure 3.1 Cerebral blood flow autoregulation curve. Reproduced from (42).

The ATLS management of head injured patients relies on the Glasgow Coma Scale following resuscitation. Patients with a mild head injury (GCS 13 to 15) should be admitted to a hospital ward and regular neurological observations made and the appropriate action taken if there is a change in neurological status. All patients with a GCS of less than 13 should have a computerised tomography (CT) scan of their head. Those with severe head injuries will be intubated and ventilated and on full cardiorespiratory support in an intensive care unit with neurosurgical teams available should the patients need any sort of neurosurgical intervention. The decision to operate on a head injured patient is based on various factors in the history including the premorbid state and GCS at the scene of the accident (i.e. severity of injury), onset and rate of neurological compromise. These would be supported by radiological findings on accompanying CT scans. (43)

The aim in the treatment of head injured patients is to maintain an adequate cerebral perfusion pressure, reduce intracranial pressure and cerebral oedema. This is aided in part by keeping physiological parameters as ideal as possible to aid in recovery e.g. normoglycaemia, nutritional and haemodynamic support; keeping normal or low carbon dioxide levels, temperature control, patient positioning to avoid venous

congestion and raising ICP. (44)The one purpose of brain monitoring, is to detect secondary insults and to be able to intervene early if appropriate. (45)(46)(47)

3.4 Monitoring the brain

3.4.1 Intracranial pressure

Intracranial Pressure (ICP) is defined as the pressure within the rigid cranial cavity relative to atmospheric pressure.(48) Normal ICP ranges from 5-15mmHg in a resting healthy adult in the horizontal position. There is a vascular component as well as a cerebrospinal fluid (CSF) component.(49) It is pulsatile and reflects the cardiac and respiratory cycles. An ICP of more than 15 mmHg is considered abnormal. There are different waveforms seen with an ICP trace (Table 3.2), with differing amplitudes and associations as illustrated.

	Associated with	Amplitude	Duration
A (plateau) waves	Cerebral vasodilatation Reduced cerebral compliance	50-200 mm Hg	5-20 min
B waves	Changes in respiratory pattern	<50mm Hg	1 min
C waves	Blood pressure and systemic vasomotor tone	<20 mmHg	7-15s

Table 3.2 Different waveforms seen in an ICP trace. Adapted from (35).

Figure 3.2 illustrates how cerebral blood flow is autoregulated. As blood pressure increases, cerebral blood flow is maintained at a constant until a critical point beyond which the brain will develop ischaemia and be prone to damage.

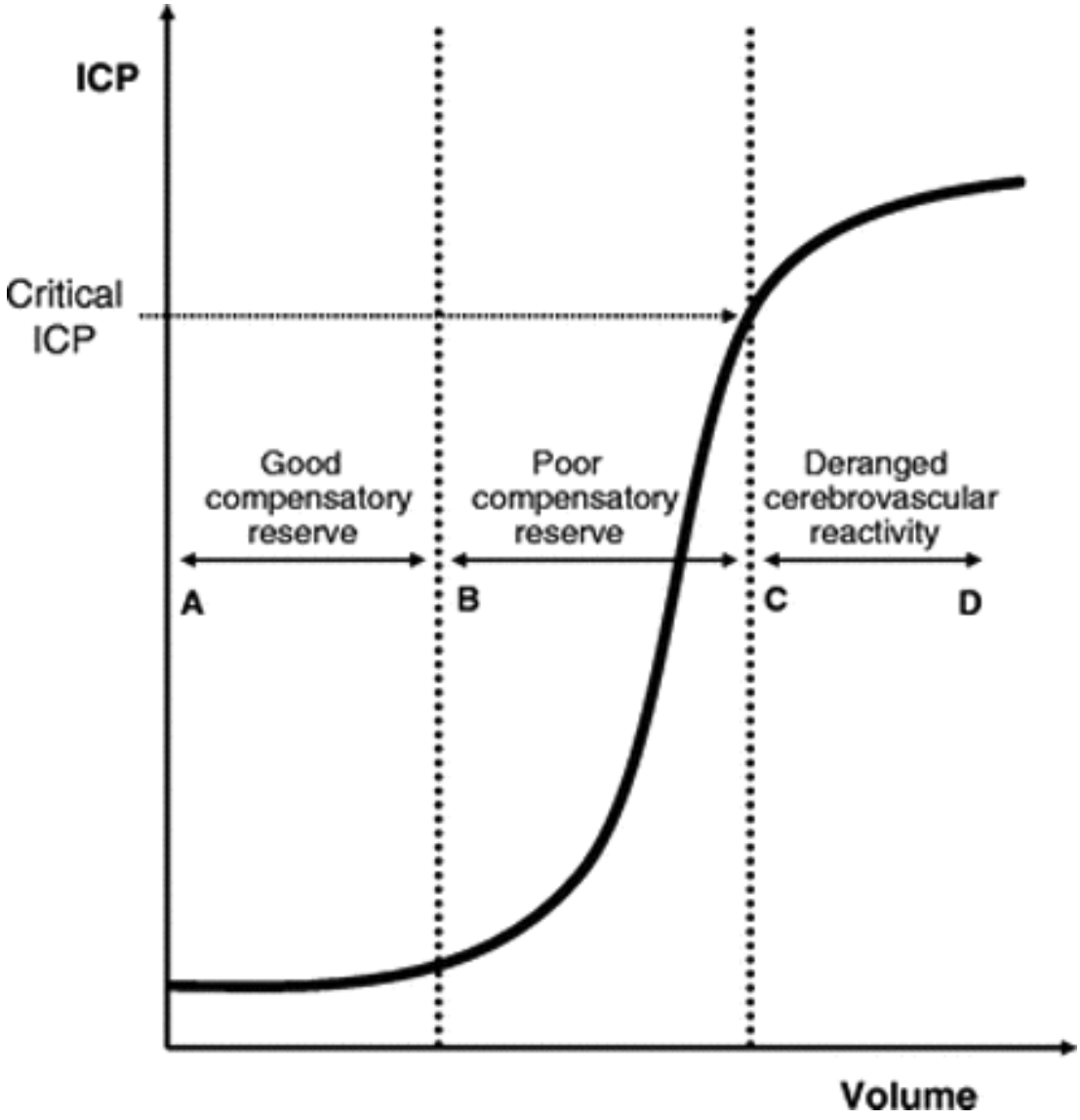


Figure 3.2 ICP-volume curve. Reproduced from (50).

Prolonged rise in ICP is associated with a poor prognosis in head injured patients, and early treatment decreases mortality in these patients. In head injured patients, a rise in ICP of more than 20 mmHg usually demands treatment, depending on the underlying pathology, rate of deterioration and clinical circumstance. Thus a device for monitoring ICP is needed for such patients to detect any early changes in ICP that may need surgical intervention, for example, an enlarging haematoma that could be evacuated.

Measuring the ICP allows:

1) Continuous monitoring of pressure changes within the cranium. Acute rises in ICP occur when the normal compensatory mechanisms fail.

2) Analysis of the ICP waveform (Table 3.2): This provides information about transmission of the arterial pulse pressure through the arterial walls to the CSF space. As cerebral perfusion pressure (CPP) decreases, the wall tension in reactive brain vessels deceases as well, this in turn increases transmission of the arterial pulse to ICP. In normally reactive vessels, a decrease in CPP should invoke an increase in arterial blood pressure to ICP pulse transmission.

- A (plateau) waves: amplitude 50–100mmHg, are usually most common in patients with intracranial tumours and represent severely reduced intracranial compliance.
- B waves: amplitude <50mmHg, occur about one per minute, and associated with respiration. Less useful clinically. Variations of B waves called 'ramp' waves are seen in hydrocephalus
- C waves: amplitude <20mmHg, about 4–8 occur per minute. These are related to systemic vasomotor tone and blood pressure and again not useful clinically.

3) Estimation of cerebral perfusion pressure: CPP = MAP(mean arterial pressure)-ICP. Thus increasing MAP raises CPP and raising ICP reduces it. The normal CPP is usually between 70–90mmHg in an adult. A lowering of CPP below 70 mmHg will lead to ischaemic brain damage. In the normal brain, CPP is maintained by autoregulation, within the limits of a MAP of 60–160mmHg. Autoregulation may be impaired by the head injured brain.(51) ICP is usually measured with devices placed in a ventricle, subdural space or directly into brain parenchyma. The various methods for monitoring will be listed and expanded on below:

3.4.2 Intraventricular catheter

The gold standard for ICP measurement is the intraventricular catheter, which is inserted into the lateral ventricle via a burr hole. It can be used to remove cerebrospinal fluid (CSF) and to give drugs e.g. antibiotics. It can be connected to an external pressure transducer. However, insertion maybe difficult in cases where there

is a lot of cerebral swelling. Infection rates are of the order of 1–5% and increases significantly with time. (52)

3.4.3 Intraparenchymal monitors

There are other ventricular, subdural or intraparenchymal microtransducers that can be inserted via a burr hole such as the Camino transducer, which makes use of a fibreoptic cable to direct light to a miniature displaceable mirror at the catheter tip, which is placed in brain tissue. ICP distorts this mirror and the reflected light intensity is transduced into pressure. Available also is a microchip Codman strain-gauge sensor which can be inserted into the brain via a small burr hole, which converts resistance changes, due to ICP, into a voltage change.(53) These are deemed to be almost as accurate as ventricular drains and have relatively low rates of infection and bleeding. They are useful when the ventricles are inaccessible because of compression from raised ICP. The main disadvantages are that they cannot be recalibrated *in vivo*, and they measure localised pressure, which may not be an accurate reflection of ICP. CSF drainage is not possible, and they are subject to drift when used for prolonged periods.

Subdural pressure transducers are the least invasive of the lot. The dura is pierced and the hollow device is filled with CSF; once equilibrium is reached, the pressure transduced is a reflection of ICP. However, this is not as accurate as the gold standard, and again CSF cannot be drained with this device and is subject to blockage and misplacement. It does possess a lower risk of infection and bleeding rate.

3.4.4 Jugular bulb oximetry

The jugular bulb, located in the internal jugular vein, just below the base of the skull, receives blood directly from the brain. Measuring the oxygen content of this blood allows the estimation of cerebral oxygen consumption. (54)

This involves inserting a retrograde catheter into the internal jugular vein and advancing it cephalad into the jugular bulb. Correct placement is confirmed by a lateral neck x-ray when the tip should be at the position of the mastoid air cells at the level of the first and second cervical vertebrae. The catheter contains a spectrophotometric fibreoptic probe and a lumen for aspiration of blood. Infrared light at three wavelengths measures haemoglobin concentration and oxygen saturations. Measurement of jugular venous oxygen saturation ($SjvO_2$) can thus be made, and is normally of the range 60–75%. A value of less than 50% may indicate potential cerebral ischaemia. $SjvO_2$ is dependant upon arterial oxygen saturation, cerebral blood flow and cerebral metabolic rate. It is used for the management of severe head injury, and is able to indicate how effective any intervention maybe, e.g. minimising the use of vasopressors to maintain an adequate CPP. (46)(55)

Intermittent sampling will allow estimation of arteriovenous oxygen difference and lactate and give an indication of global cerebral oxygenation and metabolism. Continuous $SjvO_2$ monitoring will detect episodes of desaturation associated with raised ICP e.g. hypotension, cerebral vasospasm, hyperventilation therapy. However, there is a false positive rate of up to 50%. It is also a measure of global cerebral oxygenation rather than regional oxygenation, and smaller areas of ischaemia could go undetected. The other limitations are the difficulties in obtaining accurate readings (due to difficulty in placement or too rapid an aspiration of the blood sample) and their interpretation. Inaccuracy can also result if the catheter is impacted against a vessel wall or if thrombosis occurs. Frequent calibration is also required and protein build-up at the catheter tip can lead to further inaccuracies. As this monitor is invasive and can lead to local complications, current recommendations are that $SjvO_2$ monitoring is used as a second-line device to help guide the treatment of raised ICP refractory to standard treatment. (56)(57)

3.4.5 Transcranial Doppler ultrasonography

Transcranial Doppler is a non-invasive ultrasound based technique which measures blood velocity in the cerebral arterial system. A 2 MHz pulsed ultrasound signal is transmitted through the skull, usually via the temporal bone, to a depth of 5–6.5 cm.

The signal is reflected by the solid components of blood and is distorted according to the Doppler shift. The pulsatile waveform obtained is a reflection of the distal cerebral vascular resistance, providing there is no stenosis or vasospasm and that blood pressure remains constant. The main uses are:

1. To differentiate between vasospasm and hyperaemia in patients with subarachnoid haemorrhage and brain injury.
2. To determine the adequacy of collateral circulation during carotid surgery.
3. Monitoring of patients who have had strokes; detection of micro emboli in the circulation.
4. Estimation of perfusion pressure.

In patients who have had a subarachnoid haemorrhage, the object of transcranial Doppler ultrasonography is to detect elevated flow velocities in the basal cerebral arteries suggesting vasospasm, and thus helping to identify patients at risk of developing delayed neurological effects. The transcranial Doppler is most reliable in detecting vasospasm of the middle cerebral artery. The reported positive predictive value is high (100%) whereas the negative predictive value is low (30%) when angiography is used as a reference standard. On the other hand, the positive predictive value is low (39%) whereas the negative predictive value is high (90%) when symptomatic vasospasm is used as a reference standard. Due to differences in anatomy and the lack of correlation between flow velocities and lumen diameter, and the presence of collateral blood flow, the transcranial Doppler is less reliable in detecting vasospasm in the major cerebral arteries apart from the middle cerebral artery. Blood flow and vessel diameter may be directly measured using the transcranial Doppler. The device is useful in deciding whether a clinical condition is deteriorating due to a result of vasospasm or if other causes should be excluded by performing a detailed CT scan. One of the major advantages is its ease of use by the bedside and its non-invasive nature allowing for repeated measurements. Its major limitations are that it is highly operator dependent and has no strong correlation between flow velocities measured and delayed neurological defects. (58)(59)

3.4.6 Near-infrared cerebral spectroscopy

Near-infrared spectroscopy (NIRS) offers a non-invasive monitor of brain oxygenation. It is based on molecular overtones and combination variations. A sensor is placed on the patient's forehead and shines infrared light (700–1000 nm) through the surface layers of the brain and the light that re-emerges is sensed by a dual detector system. The absorption of near infrared light is proportional to the concentration of certain chromophores, such as the iron in haemoglobin and copper in cytochrome aa3. Oxygenated haemoglobin, deoxygenated haemoglobin and cytochrome aa3 have different absorption spectra, depending on the patient's oxygenation status. Changes in concentration of near infrared light as it goes through these compounds are quantified using the Beer-Lambert law, which describes optical attenuation. (60)(61)

Instrumentation for NIRS is somewhat similar to instruments in the infrared and mid-infrared range. There is a source and disperser (usually a prism or diffraction grating) to allow intensities of light of different wavelengths to be recorded. Common incandescent light bulbs are often used as light sources of near infrared radiation for analytical applications. The alternatives used are LEDs, which offer greater lifetime and spectral stability and are more energy efficient.

The advantages of NIRS is that it is a non-invasive, non-ionising, pain-free means of estimating regional changes in cerebral oxygenation. (62) It is also able to estimate changes in cerebral blood volume. The monitor gives a real-time, display of cerebral oxygen levels and has been shown to correlate well with jugular bulb saturations in healthy volunteers under conditions of isocapnic hypoxia. The monitor is also highly portable (compared to MRI, see sub-section 3.4.10, and can be used in the infant population). Wireless instrumentation is also available which allows freedom of movement in the subjects being studied. By injection of a dye, indocyanine green, cerebral blood flow and cerebral metabolic rate can be calculated. Due to its safe profile, NIRS can be used in paediatric intensive care units. (63)

The disadvantages of NIRS is that the clinical use is limited by its inability to distinguish between intracranial and extracranial changes in blood flow and

oxygenation, with an effect on the accuracy of readings obtained. (64) It does remain, however, to be one of the established techniques for monitoring patients with head injury, is able to indicate cerebral hypoxia, and is available in most intensive care units that manage a large proportion of patients with head injuries. (65)Further studies are needed to establish its use in clinical practice. (66)(67)(68)

3.4.7 Brain tissue oximetry

There are two commercially available sensors to measure brain tissue oxygenation continuously. One device – Licox – measures only brain tissue oxygen tension ($PbtO_2$) using a polarographic Clarke type electrode. The other – Neurotrend – is a multi-parameter sensor that can measure brain tissue oxygen, carbon dioxide and pH using fibreoptic technology. Both of these monitors can also measure brain temperature using a thermocouple. Both sensors are approximately 0.5 mm in diameter and can be inserted through a craniotomy intraoperatively or through a specifically designed bolt allowing insertion and fixation to the skull in the intensive care unit (ITU). (69)(70)

The Licox monitor has played an important role in the implementation of multimodal monitoring in ITUs. The Licox system itself is supplied with a temperature, oxygenation and ICP probe – all three monitors are incorporated into one device.(71)The temperature probe is quoted to have an accuracy rate of up to 0.2 degrees Celsius of the current temperature of any tissue up to five days in situ. It is also able to obtain precise $PbtO_2$ values from regional areas of the brain and global ICP measurement.

Accurate placement of Licox catheters is crucial to obtaining reliable readings. These are usually put in on the right side in the subarachnoid space of the frontal lobe with the oxygen probe extending into the white matter of the brain. A CT scan of the head can be used to locate the area of damage, and the catheter can be placed within the penumbra of the injury. The Licox may take up to 120 minutes to settle before readings can be obtained. To check the probe is working properly, an increase in inspired oxygen concentration in intubated patients should see a corresponding rise

in value of $PbtO_2$. The values of $PbtO_2$ vary greatly depending on placement of the Licox as well as insults during placement into brain tissue. Low readings may be due to microvascular compression of the probe within the area of injury. Placements in contusions, infarcts, and haemorrhagic areas may adversely affect oxygen measurements and may result in low readings of oxygen measurements. As a consequence, local placement may potentially lead to either over treatment or under treatment of viable brain tissue because of the limited information provided on surrounding areas. Likewise, placement of the probe in undamaged areas reflects changes in global oxygenation. $PbtO_2$ readings are indicative and influenced by oxygen exchange within the capillary beds and by the diameter of the vessels that surround the catheter. After placement, the probe can take up to 80 minutes or more to adapt to brain tissue and to give accurate recordings. (48)

The Licox is stable in brain tissue for up to 16 days, and recalibration is unnecessary. The Licox probe is contraindicated in coagulopathic states; the risk of infection or a contusion produced by the placement of a Licox monitor is less than 2%. The Neurotrend (Codman) system uses "optimal luminescence" to measure $PbtO_2$. It also measures pH, tissue CO_2 and temperature. It has a faster response time (compared to the Licox) to changes in oxygen concentration, and measured pH and $PbtO_2$ accurately. However, it is not as accurate as the Licox probe at lower oxygen concentrations and more prone to drift over time. (71) Brain oxygen oximetry is an invasive technique with the small risk of infection as a potential complication. The true diagnostic and prognostic value so far remains to be unreported with its impact on patient outcome undetermined.

3.4.8 Microdialysis

Cerebral microdialysis allows continuous online monitoring of changes in brain tissue chemistry. Most biochemical and metabolic events take place in the tissues, thus the function and pathophysiology of the brain is a reflection of changes in extra or intra- cellular molecular biology. Thus, being able to directly analyse tissue chemistry in the brain, could provide valuable data for patients with pathology of brain tissue. Microdialysis was first developed in the 1960s and has been changed

from a ‘bench to bedside’ technique. In microdialysis, a fine coaxial catheter (diameter 0.62 mm) is inserted into the brain. The catheter has a polyamide dialysis membrane on its outer surface and low flow rates (0.1–2.0 mcl/min) of dialysis fluid are passed through the catheter using a precision pump, allowing measurement of the concentration of chemicals in the cerebral extracellular fluid. Molecules below the size of about 20000 Daltons diffuse through the semi-permeable membrane which is collected into vials which are changed every 10 to 60 minutes. The collected dialysate is then analysed by sensitive assays. The main substances, which are of interest in the head injured patient, are:

1. Energy related metabolites e.g. glucose, lactate, pyruvate, adenosine, xanthine.
2. Neurotransmitters e.g. glutamate, aspartate, GABA (gamma-amino-butyric-acid).
3. Markers of tissue damage and inflammation e.g. glycerol, potassium, cytokines.
4. Exogenous substances – administered drugs.

Bedside equipment, allowing spectrophotometric analysis of chemicals of interest is commercially available. Cerebral microdialysis has been used in various other clinical scenarios, apart from head injured patients, such as subarachnoid haemorrhage, epilepsy, ischaemic stroke, tumours, and during neurosurgery. In severely head injured patients, deranged metabolism results in lower brain glucose and elevated lactate: pyruvate ratios during periods of intracranial hypertension and cerebral ischaemia. In patients with traumatic brain injury, any increases in lactate: pyruvate levels correlates with the severity of symptoms and clinical outcome. Wide variations in the concentration of glutamate and aspartate have been observed.

Epileptic foci in the temporal lobe are associated with elevated glutamate and lower GABA levels prior to seizures and increases in both amino acids during seizures. If microdialysis catheters are implanted in relevant positions in relation to affected tissue, this technique can give prompt information on metabolism and its consequences for cell survival. One of the usefulness of this technique is that the

biochemical changes that are detected by intracerebral microdialysis appear before significant increases in intracranial pressure.(73)

An evolving role of microdialysis is its use in measuring drug concentrations in brain tissue and the potential to be able to give drugs directly into specific areas. There are important limitations to the technique; one is that unless the microdialysis catheter is placed in the area where tissues are damaged, abnormal changes may not be detected. (74)(65) Whether the use of microdialysis, in clinical practice, will be routine is still not fully established.(75)

3.4.9 Electrophysiology

The electroencephalogram (EEG) is obtained from spontaneous electrical activity of the brain and is generated mainly by summation of excitatory and inhibitory post-synaptic potentials of cortical neurones. The technique is non-invasive and the changes in EEG correlate closely with cerebral metabolism and ischaemia. The electrical trace is obtained from scalp electrodes placed at inter-electrode distances of either 10% or 20% of the head circumference, or inter-aural distance. The electrical signal is amplified, filtered and then displayed as either eight or sixteen graphs, with eight graphs per hemisphere, to give an accurate representation of the activity throughout the cortex. EEG is usually interpreted in terms of frequency (Table 3.3) amplitude and location. (48)

Band	Frequency	Clinical State
Delta	<4 Hz	Deep sleep, anaesthesia, cerebral ischaemia
Theta	4-8 Hz	Normal waves in premature infants/children in deep sleep
Alpha	8-13 Hz	Alert, relaxed individuals with eyes closed
Beta	>13 Hz	Typically seen in alert awake adults and during light anaesthesia

Table 3.3 EEG waveforms of the brain. Adapted from (35).

To enable continuous EEG monitoring, several automated processing systems are available:

- Power spectral analysis allows rapid Fourier transformation of small intervals of EEG to give a graphical representation of the relative power content of the different frequency bands in each segment. The spectral analysis gives a single reading (e.g. mean frequency) which can be followed over time.
- Cerebral Function Monitor (CFM) gives a single trace of total power varying with both amplitude and frequency of raw EEG data.
- Cerebral Function Analysing Monitor (CFAM) which displays both amplitude and frequency and avoids the loss of information when these two variables are processed together.

The EEG is most commonly used to investigate, diagnose and manage epilepsy as well as other conditions such as subacute sclerosing panencephalitis. It can also detect ischaemic cerebral insults, such as vasospasm and intracranial hypertension after head injury. Certain EEG features are associated with poor outcome in patients. Grade I and II are associated with a good outcome, grade III with an intermediate outcome, and grades IV and V are associated with a very poor outcome. (35) See Table 3.4 below.

Grade I	Dominant α, reactive
Grade II	Dominant θ-δ, reactive
Grade III	Dominant δ-θ, no α
Grade IV	Burst suppression low voltage δ, unreactive, periodic general phenomena
Grade V	Very low voltage EEG, isoelectric EEG

Table 3.4 EEG interpretation.

Although various EEG signal processing and display systems have been used in routine monitoring of head injured patients during intensive care, they are not currently in widespread use. (73)(76)(77) The main limitations of this technique are the vulnerability to artefacts and reliance on trained neurophysiologists to interpret

results. Currently, EEG is used intermittently as a bedside diagnostic tool in patients with its true influence on patient outcome undetermined. However, improvements in terms of inclusion of digital processing and automated analysis might expand and establish its usefulness in neuro- intensive care particularly if used in conjunction with other devices such as the Bispectral Index Monitor (BIS). (78)(79)

3.4.10 Computerised tomography scans

Computerised tomography or CT scans make use of ionising radiation to produce detailed (2-dimensional) images of structures inside the body. It is used to supplement information obtained by traditional X-rays and ultrasonography techniques by giving clearer and more detailed imaging. A CT scan of a patient with head injuries can diagnose or exclude tumours, haemorrhage, fractures, or areas of infarction. The modern CT machines can produce detailed images within minutes unlike a MRI scan (refer to next sub-section 3.4.11) which takes much longer in comparison and requires a patient to be able to remain still for a prolonged period of time. CT scans are good for visualising bony structures as well as blood vessels and bowel. Contrast agents can be given to enhance the images obtained. As with any scan that makes use of ionising radiation, caution must be excised when it is used in children, pregnant women and those who require repeated CT scans. (80) CT scans are generally more widely available and cheaper than MRI scans.

3.4.11 Magnetic resonance imaging

Magnetic resonance imaging (MRI) is a non-invasive method of providing detailed imaging of body cavities. It uses a powerful magnetic field (anything from 1 to 4 Tesla), to align the hydrogen molecules in body water in the direction of the field. A radiofrequency emitter is switched on to produce an electromagnetic field, at resonant frequency, to flip the spin of the aligned protons of hydrogen. When the field is switched off, the protons decay and give off photons. These photons produce the energy that is detected by the scanner. An image is built as these photons in different tissues return to their equilibrium states at different rates. By changing the parameters on the scanner this effect is used to create contrast between different types of body tissue or between other properties. Contrast agents may be injected

intravenously to enhance the appearance of blood vessels, tumours or inflammation. Contrast agents may also be directly injected into a joint in the case of MRI arthrogram imaging of joints. Unlike CT scanning which makes use of ionising radiation, MRI scanning is generally very safe and provides better contrast resolution compared to CT scanning which provides better spatial resolution. The disadvantage of MRI is that scanning takes a considerably longer period of time than a CT scan and requires the subject to remain still for a considerable length of time in an enclosed space. The strong magnetic field can affect the function of some metal implants such as pacemakers or cochlear devices, and the presence of certain metal objects in situ in body tissues may be an absolute contraindication to having an MRI scan. (78)(79)(80)

None of the above techniques are without their limitations, and none were made for the purposes of measuring brain tissue oxygenation per se. The development of a new device, able to make use of fibreoptic technology, to obtain signals that could measure oxygen saturation in the brain and other body tissues, is an exciting prospect, which could potentially transform the next decade of monitoring the injured brain.

A device capable of giving accurate, real-time, reliable readings of oxygen saturation within the human body does not exist at present. In particular, in relation to an organ such as the brain, which is highly sensitive to hypoxia induced damage; a simple bedside monitor that could help indicate areas of ischaemia would be invaluable. This would contrast with the need for repeated, time consuming and expensive head CT or MRI scans. It would not be cost effective or practical to have an MRI scanner in every hospital. In most hospitals that house a scanner, there is usually a need to transport the patient to a site remote from the ICU; the scan requires critical care skilled staff to escort the patient on a potentially hazardous journey in order to achieve this. It is difficult to maintain stability of the patients' condition with logistical issues of moving ventilated patients with many lines and monitoring connections. So in reality MRI/CT scans are usually reserved for the occasion when a patient is deteriorating. It would also be an inappropriate use of resources to have a dedicated MRI scanner for ITUs in District General Hospitals. Most such scanners are manned in major trauma centres or neurosurgical centres.

3.4.12 Positron emission tomography

Positron emission tomography (PET) scanning is a nuclear imaging technique which produces a 3-dimensional colour image of functional processes in the body. Gamma rays are emitted by a tracer (positron emitting radionuclide) which is tagged onto a naturally occurring substance found in the human body, such as glucose, water or ammonia. A commonly used substance is flurodeoxyglucose (FDG) which can be tagged onto glucose. Cancers or abnormal growths that utilise glucose in the body in a different way than normal tissue show up as an abnormality on a PET scan. As the radiotracer is broken down in the body, the energy emitted produces a 3-dimensional image on a monitor. PET scans are usually used in conjunction with MRI or CT scans to gain additional information about a diagnosis as well as how effectively a treatment is working. (84)

In imaging of the brain, PET scans are useful for diagnosis of movement disorders such as Parkinson's and Huntington's as well as epilepsy. Images can be obtained by using a radiotracer (oxygen molecule) in water which is taken up by the brain and a reflection of blood flow; and also by glucose metabolism using deoxyglucose. Blood flow and glucose uptake produces images on PET scanning that locate seizure activity in the brain. In most patients, blood flow and glucose uptake is increased in the cerebral cortex during seizure activity and reduced in the period between seizures. In the patient with a head injury, areas of brain damage have reduced blood flow and glucose metabolism.(85)

3.4.13 Summary

In combination with existing methods of monitoring the head injured brain, this fibreoptic probe (described in the next chapter) could add to the way we monitor patients with head injuries. The probe in question, looks at specific, focal areas of oxygenation in the brain, compared to the current global options that are used in clinical practice. It is implemented via existing conduits which are in regular use on neuro-intensive care units; measurement is not a direct assessment of brain function – we make assumptions regarding the likely thresholds of e.g. ICP/Systemic blood pressure, when the brain might be at risk of secondary damage. Hence an area of need for a monitor capable of real-time direct brain oxygen saturation readings.

3.5 Oxygen saturation measurements from brain tissue – on neurosurgical patients undergoing elective surgery

After severe head injury, neurosurgery and a number of critical illnesses, the supply of blood and oxygen to the brain may be compromised, causing brain damage and possibly death. Clinical signs may be too late or unclear, hence the need exists for a reliable monitor and early warning system to detect such deteriorations. From the introduction, we know that there is no reliable way of determining what really goes on inside the human brain. Mechanisms of either head injuries or neurological pathologies such as brain tumours manifest in different ways. Given the barriers to brain monitoring presented by the vessel rich scalp, the relatively opaque skull and the potential severity and life-threatening nature of these conditions, invasive monitoring techniques are deemed appropriate and in many specialist centres, are routinely used. At The Royal London, one of the leading trauma centres in the United Kingdom, ICP monitoring probes are passed onto or into the brain via an 'intracranial bolt', a hollow metal tube (approximately 0.5 cm diameter), which is screwed into the skull and has 2–3 channels through which the probes are introduced. These allow for monitoring of ICP in patients with unstable head injuries, and trends or changes in ICP indicate the need for further investigations or treatment.

After several discussions with the engineers at City University, we approached neurosurgeons and intensive care doctors at The Royal London, on their views on a probe that could measure oxygen saturation in brain tissue. It was agreed that this would have great research value as well as the potential to develop into a novel bedside tool for monitoring patients with neurosurgical pathology. In order for the idea to work, it had to be of the correct size and dimensions to fit the lumen of the cranial bolt that was in routine use on the intensive care unit (ITU) at The Royal London Hospital.

With this in mind, this fibreoptic probe was constructed by a member of the Biomedical Engineering Research Group, City University, London, with a view to evaluating its use in patients. A pilot study was needed to determine whether adequate photoplethysmographic (PPG) signals could be obtained from the brain tissue and to determine the optimal optical fibre characteristics and depth of

penetration of fibres to the brain. If good PPG signals could be obtained, this would then allow us to obtain readings in longer durations measurements e.g. for patients on the intensive care unit. The protocol for the study was written and ethics and MHRA application sort for this in mind. We also needed to liaise with the hospital's sterile services department to ensure that the single-use only probes would be sterile for insertion into human tissue.

3.6 Aims

The primary aim of this study was to determine whether adequate PPG signals could be obtained from the brain tissue. The study also aimed to verify whether the cranial bolt access system could serve as a suitable conduit for the fibres and whether the acquired signals would be adequate for calculation of oxygen saturation. The secondary aims were to assess the accuracy of the system, and feasibility for longer-term measurements. [Later on, measurements of longer duration were also taken from a single patient suffering with an acute intra-cerebral haemorrhage in The Royal London Hospital ITU; this will be discussed in section 3.10].

3.7 Protocol and ethics approval

We had full local research ethics committee approval as well as full MHRA approval for use of the probe. A pilot study was undertaken intra-operatively in neurosurgical patients at The Royal London Hospital, in order to determine whether PPG signals could be obtained from the brain tissue, and to determine the optimal optical fibre characteristics and depth of penetration of the fibres into the brain (see Appendix A).

3.8 Materials and methods

In this study, a dual wavelength optical fibre PPG system was used. The probe consisted of two silica optical fibres with a core diameter of 400 μm and a numerical aperture (NA) of 0.39. Each fibre is terminated at one end with an SMA connector and the other end is cut and polished flat. The fibres are covered in a protective PVC jacket, which is stripped away over a length of 16 cm from the distal end. The probe

materials are biomedically compatible, and can undergo steam sterilisation at 136 degree Celsius. The instrumentation is housed in a metal box containing: red (660 nm) and infrared (850 nm) emitters (LEDs), a PIN photodiode photodetector, a battery power supply and a simple signal processing circuit. The signals for each of the two wavelengths are recorded and stored on a notebook computer using a LabVIEW (Laboratory Virtual Instrument Engineering Workbench) based data acquisition system. (Figure 3.1)

LabVIEW is a programme development environment that utilises a graphical programming language, G, to create programmes in the block diagram form. It relies on graphical symbols, rather than textual language (C, C++, Java) to describe programming actions. It is especially suitable for instrument control, data acquisition, and pre/post processing of acquired data. LabVIEW programmes are called Virtual Instruments (VIs) because their appearance and operation imitate actual instruments. The LEDs (light emitting diodes) were both connected to the single optical transmitting fibre using a Y- coupler (a bifurcated optical fiber assembly from Ocean Optics Inc., Dunedin, FL, USA). The photodetector is coupled directly to a receiving optical fibre.

An instrumentation unit is used for the control of the light sources and acquisition of signals from the tissue. This hardware is interfaced to a 16-bit DAQCard-AI-16XE-50 data acquisition card (National Instruments Inc. Austin, TX, USA) and installed into a notebook computer. The LEDs are driven by a pair of switchable regulated current sources, one for each wavelength, supplying 25 mA and 14 mA to the red and infrared LEDs, respectively. Timing signals are provided by a programmable counter timer built into the data acquisition card.

The photodiode is connected to a differential transimpedance amplifier. The output of the transimpedance amplifier is fed into a demultiplexer and the signals separated into three components, representing the infrared (IR), red (R) and ambient (AMB) light intensities. Any high frequency noise is filtered. The instrumentation is powered by two 12 V 1.2 Ah sealed lead-acid batteries. The signals are all fed into the analog-to-digital converter built into the data acquisition card installed in a notebook computer running a LabVIEW software (National Instruments Inc. Austin, TX,

USA) Virtual Instrument (VI). The VI reads the digitized signals at a rate of 100 samples per second and records the signals in a spreadsheet file. Figure 3.3 shows a photograph of the system.

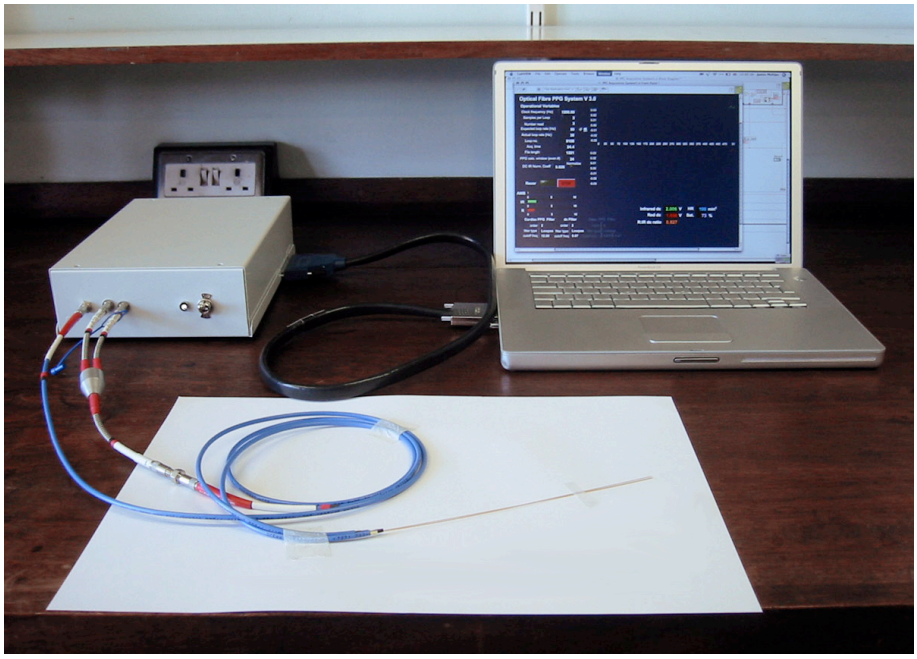


Figure 3.3 Photograph of the measurement system, with fibreoptic cables all linked to the notebook computer for recording of signals.

This fibreoptic probe had also undergone stringent testing with clinical physics for electrical safety and deemed safe and appropriate to be used in this clinical setting. The Integra Neurosciences IM-3 Cranial Access System was used in conjunction with the fibreoptic probe. This allowed the tips of the optical fibres to be placed directly within brain tissue. The IM-3 system is designed to accommodate three sensors: an intracranial pressure sensor, a Licox tissue oxygen partial pressure sensor and a temperature probe. The Licox and temperature lumens were suitable for the insertion of two optical fibres. The IM-3 system comes in a sterile package containing a threaded cranial bolt, triple lumen insert and tools to aid insertion of the bolt. Essentially, the bolt is fixed into place after burr holes are made, depending on the location of the pathology, by the neurosurgeons, under sterile surgical conditions. The bolt is screwed into the burr hole until the thread is almost concealed by the skull. The triple-lumen insert is passed through the lumen of the bolt so the distal end penetrates the brain tissue. A compression cap, attached to the body of the insert, is

tightened onto a thread on the rear of the cranial bolt, compressing a hollow cylindrical silicone washer in the assembly. This washer expands, achieving a tight seal between the assembly and the bolt. Figure 3.4 below shows a close up picture of the IM-3 cranial access kit.

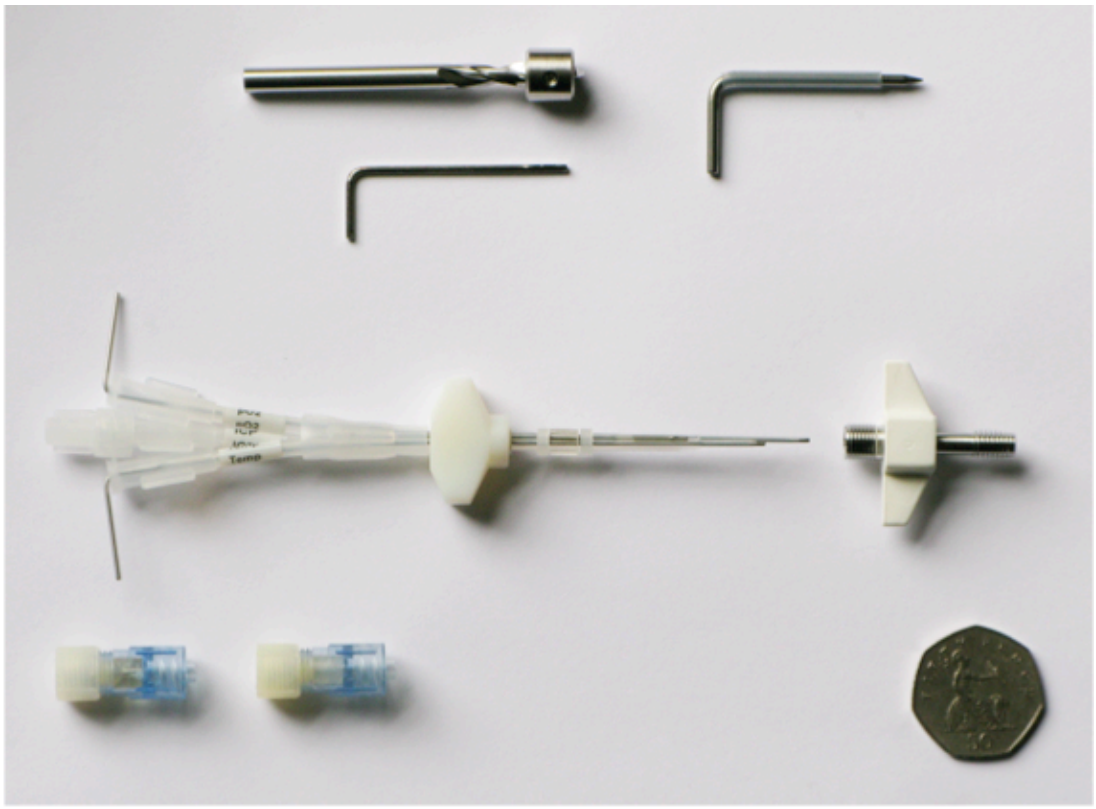


Figure 3.4 IM-3 cranial access kit with the cranial bolt, drill bit, insert, dural perforator and self-sealing leur caps. A fifty pence piece is shown for scale.

There are luer hubs at the proximal end of the triple-lumen assembly with special inter-locking luer caps. Each cap has a patent channel through which the corresponding probe can be threaded. Tightening the cap causes longitudinal compression of a silicone washer, which expands inwards producing a seal around the probe. A cross sectional diagram of the bolt in situ is shown in Figure 3.5. A photograph of the bolt with fibres is shown in Figure 3.6. The intracranial bolt is designed to be left in place for several days enabling ICP and other measurements to be made for the length of time that is needed in a critically ill patient.

Written, informed consent was obtained from patients undergoing elective neurosurgery, at The Royal London Hospital, Whitechapel. They patients were all

given a general anaesthetic and their airway secured. They were all intubated and their lungs mechanically ventilated for the operation. A triple-channel IM-3 integra cranial bolt was inserted by the neurosurgeon undertaking the operation. The neurosurgical patients only received a bolt temporarily as they invariably required a craniotomy (removal of a small part of the cranium). The most common operations were the removal of tumours or clipping of aneurysms. In order to perform a craniotomy, one or more burr-holes are initially drilled, and one of these holes was used for the temporary placement of the bolt. The fibres were then inserted via the bolt, until at a depth of 5 mm into the brain, and PPG signals were recorded for several minutes. 5 mm was chosen as a suitable depth of penetration to ensure that the detected light was entirely from brain tissue and not from any other tissue encompassing the brain. This would also ensure that the fibres protruded fully from the end of the cranial bolt assembly. As a routine part of the anaesthetic, each patient's arterial oxygen saturation was also monitored using a commercial finger pulse oximeter. After the monitoring period, the fibres and the bolt were removed and the surgery resumed.

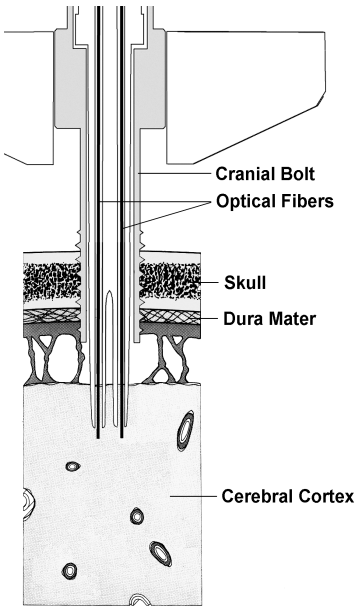


Figure 3.5 Cross-sectional diagram of bolt in situ when taking readings from the brain. Adapted from (86).

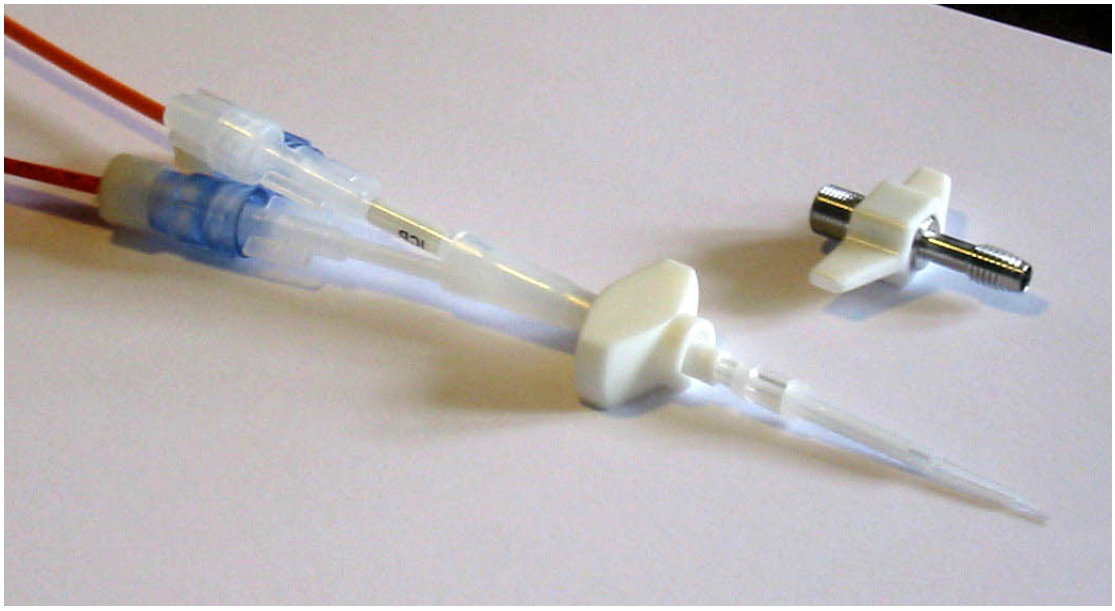


Figure 3.6 Photograph of the fibres and cranial bolt.

3.9 Results

In total, six patients (four males, two females) aged between 46 and 70 requiring elective neurosurgery were studied. An estimation of oxygen saturation was made by retrospectively analysing the red and infrared samples. A visual inspection was done, selecting the best waveform in terms of height and amplitude and minimal artefacts. The arterial oxygen saturations were estimated from the cardiac-modulated components of the signal using a LabVIEW virtual instrument incorporating a fast Fourier transform algorithm for analysis.

The amplitude of the pulse peaks in each amplitude spectrum were then calculated and normalised by dividing by the amplitude at zero frequency (i.e. DC components) in each spectrum. The cerebral arterial oxygen saturation, $ScaO_2$ was estimated using an empirically derived formula for estimating oxygen saturation in pulse oximetry from the 'ratio-of-ratios' (enclosed within the parentheses in the Equation 3.1):

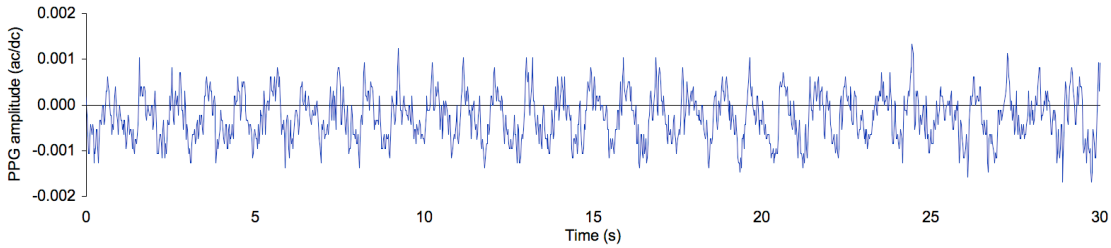
$$ScaO_2 = 110 - 25\left(\frac{A_{card,R}/A_{DC,R}}{A_{card,IR}/A_{DC,IR}}\right) \qquad (3.1)$$

where $A_{card,R}$ and $A_{card,IR}$ are the red and infrared cardiac peak amplitudes and $A_{DC,IR}$ and $A_{DC,R}$ are the amplitudes of the infrared and red spectra at zero frequency. (33)

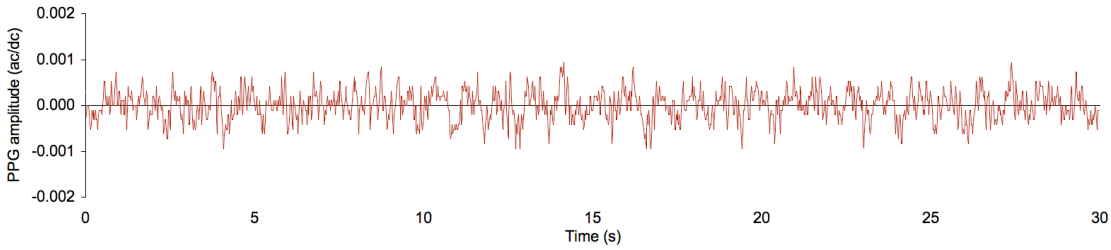
The long duration data was broken down into blocks of 60 seconds. A continual estimation of the arterial and venous oxygen saturations was produced from successive data blocks utilising the same software algorithm used for the short duration measurements. Though signals were successfully obtained from all the six patients studied, they did differ in quality between the patients. Due to this, and the relatively small sample population, the results from each patient will be described and considered separately. To compare each waveform between the patients, each waveform was divided by the total intensity i.e. AC signal divided by DC signal and the waveforms inverted. Signals were successfully obtained at both wavelengths for all patients. A sample trace obtained from each patient are shown and discussed below.

Patient One:

The first patient was a 24 year old male who needed a craniotomy for the clipping of a cerebral aneurysm. At the time of insertion of the probe, his heart rate was 62 beats per minute with a blood pressure of 122/67 mmHg and mean arterial pressure of 85 mm Hg. His peripheral SpO_2 reading was 99% throughout. Good PPG signals were obtained, with minimal artefact for more than 60% of the recording time period (total recording time of 260 seconds). A typical 30 second tracing obtained from this patient is shown in Figure 3.7.



(a)



(b)

Figure 3.7 Infrared (a) and red (b) normalised PPG signals recorded from patient number one. Adapted from (8).

Patient Two:

This second patient was a 38 year old male who required a craniotomy for the resection of a tumour. His heart was 70 beats per minute, with a blood pressure of 130/82 mmHg, mean arterial pressure of 98 mmHg at the time of recording. The peripheral SpO_2 reading was 99% throughout the measurement period. Total recording time was 276 seconds. A 30 second trace obtained from this patient is shown in Figure 3.8. There was interference with the signals for about half the period that signals were recorded. One very likely major contributing factor as the source of the interference was the Stealth Surgical Navigation System (Stealth Inc., Earlysville, VA, USA). This Stealth system is frequently used in this sort of surgery to locate and identify tumour positions accurately in the brain. Each patient has a CT or MRI scan beforehand which is fed into the Stealth imaging system. The imaging system enables the position, in 3-dimensions, of tumours to be pinpointed by a 'wand' held by the operating surgeon. The 'wand' is positioned in relation to fixed markers on the patient's scalp and the corresponding images are displayed from its database of CT or MRI scans. Thus tumours and other structures in the brain can be readily and accurately identified and located by the surgeon, to aid in the excision of the tumour. This Stealth system makes use of a pulsed infrared light source with a rate of 20 Hz.

As the pulsed periods from this Stealth system are brief in nature, interference is only detected at those intervals at which measurement of the PPG signals coincides directly with the pulsed frequency from the Stealth. The fibreoptic probe measurements occur at a frequency of 100 Hz. To counteract this problem, the use of a low pass filter system would abolish any traces of interference.

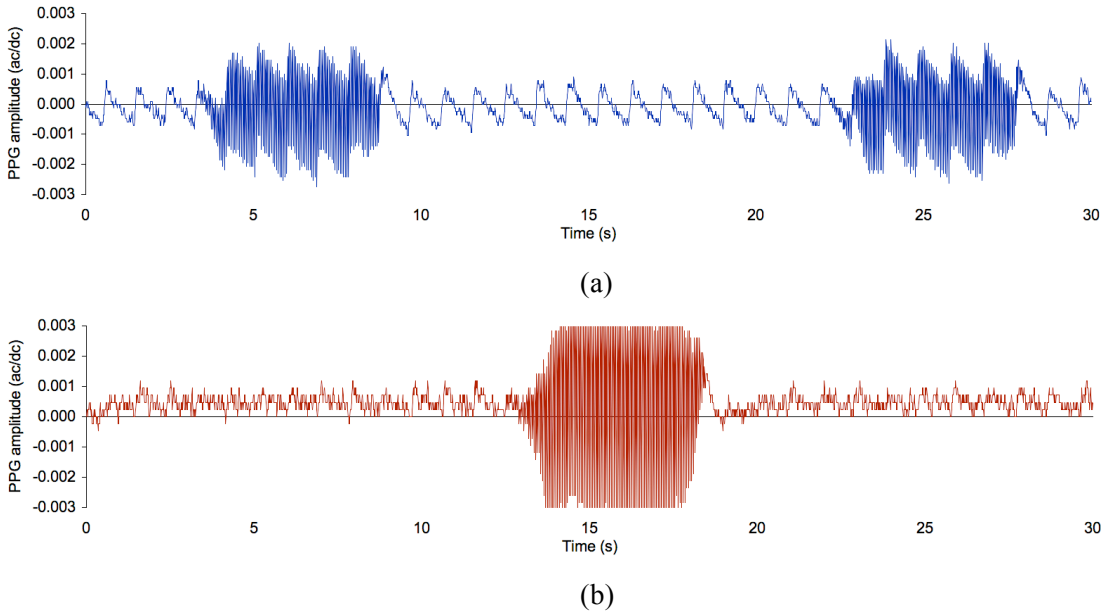


Figure 3.8 Infrared red (a) and red (b) normalised PPG signals recorded from patient number two. Adapted from (8).

Patient Three:

Patient number three was a 31 year old female patient who underwent a craniotomy for the resection of a brain tumour. This patient had a heart rate of 54 beats per minute and blood pressure of 106/58 mmHg with a mean arterial pressure of 74 mmHg at the time of the recording. The peripheral SpO_2 readings were 98% throughout. Clear signals, without interference was obtained for more than 80% of the recording. Total recording period was 286 seconds. The frequency of the interference in this patient was of low frequency and corresponded to the rate of mechanical ventilation. Thus, this interference was very likely due to ventilator induced changes in the cerebral circulation. A typical 30 second trace obtained from this patient is shown in Figure 3.9.

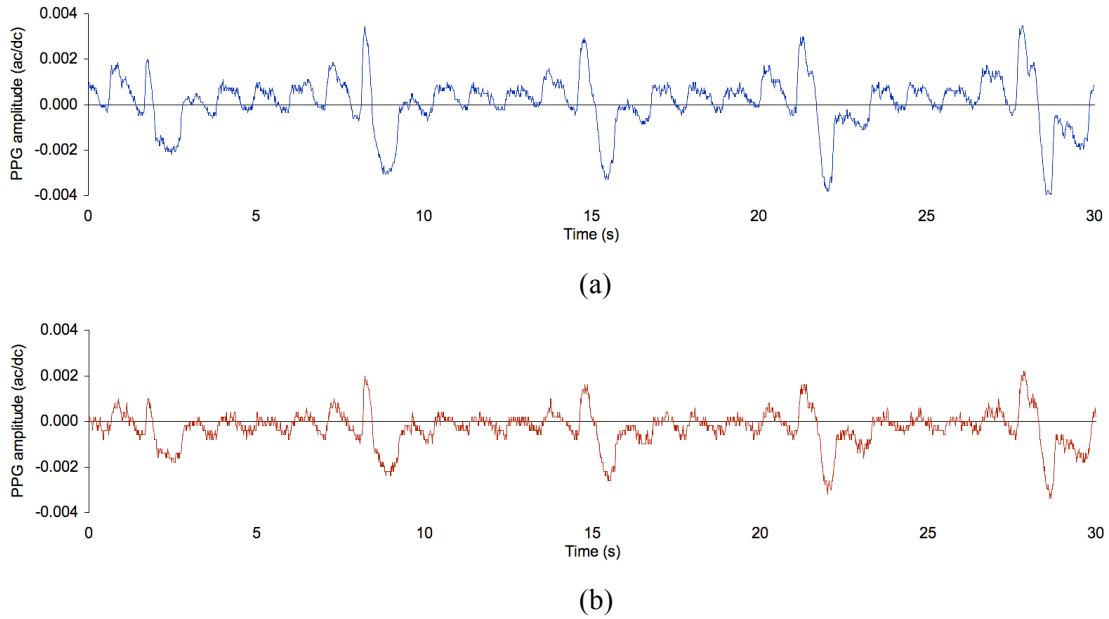
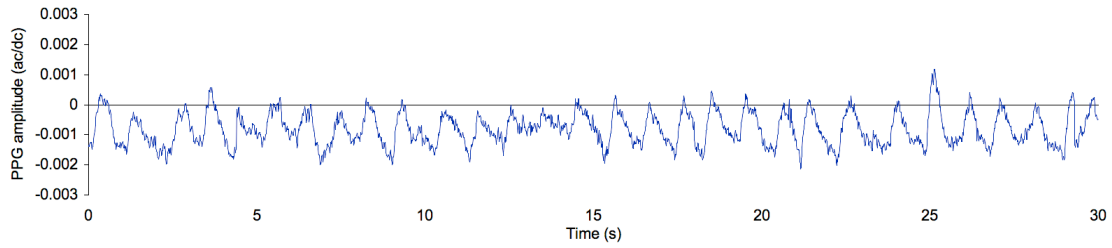


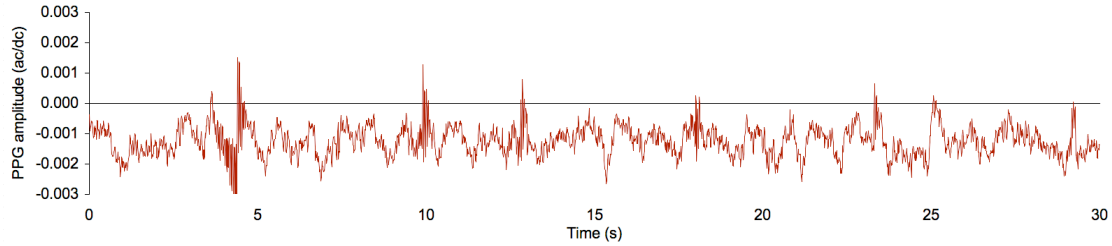
Figure 3.9 Infrared (a) and red (b) normalised PPG signals recorded from patient number three. Adapted from (8).

Patient Four:

Patient number four was a 76 year old male patient who had a craniotomy for the resection of a brain tumour. At the time of the recording, he had a heart rate of 58 beats per minute, blood pressure of 118/57 mmHg, mean arterial pressure of 84 mmHg. His peripheral SpO_2 readings were 99% throughout. Signals were obtained for a brief period (total recording time of 148 seconds) with interference in about half that time span. A 30 second trace obtained from this patient is shown in Figure 3.10. The PPG signals obtained were of poor quality in general. The reason why is uncertain. It could be that the fibres were not in far enough or that the duration of the monitoring period was not long enough. Part of the problem could be that the fibres placed by the operating surgeon was not in a region of the brain with adequate blood flow, hampered by the time factor in that the operating surgeon needed to proceed with the operation urgently, and hence the period of recording was shorter than anticipated.



(a)



(b)

Figure 3.10 Infrared (a) and red (b) normalised PPG signals recorded from patient number four. Adapted from (8).

Patient Five:

Patient number five was a 60 year old patient who had a craniotomy for resection of his brain tumour. He had a heart rate of 66 beats per minute, blood pressure of 116/55 mmHg, mean arterial pressure of 75 mmHg at the time of recording. His peripheral SpO_2 readings were 99% throughout. The signals were recorded for a total period of 525 seconds with good signals i.e.no interference for >85% of the time. There were some excellent PGG waveforms obtained with good demarcations. There was some minor interference, which corresponded to the respiratory frequency of the patient. The signals obtained here were atypical from what was expected in this patient in that the amplitude of the red PPG waveform was larger than that of the infrared one. A 30 second trace is shown in Figure 3.11. This is usually seen when the arterial oxygen saturation falls below 85% when using a standard pulse oximeter. The subsequent calculated oxygen saturation was thus spuriously low as shown in Table 3.5.

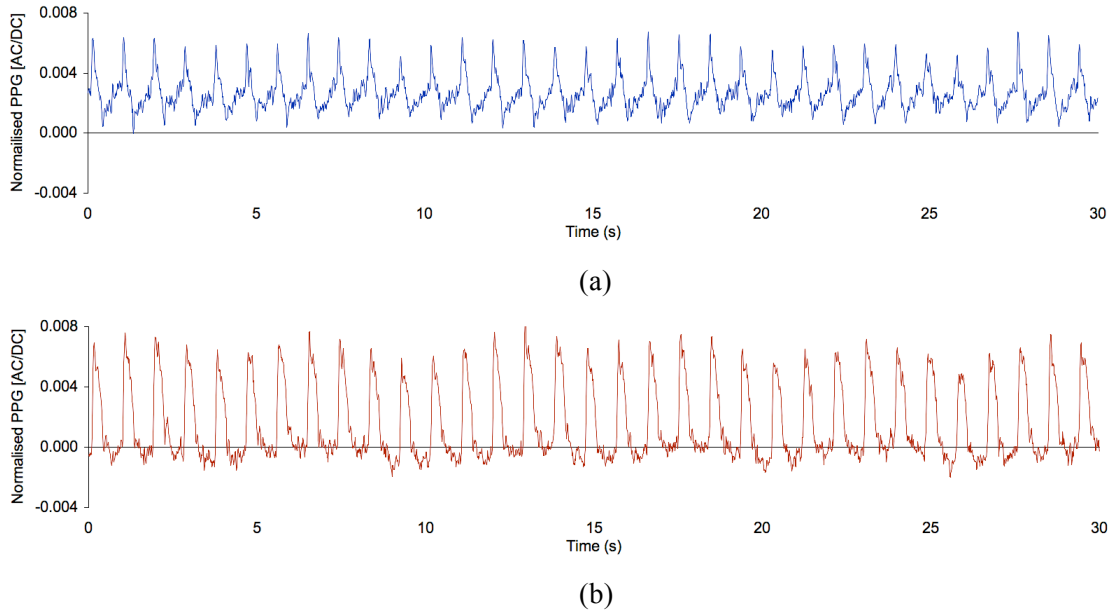


Figure 3.11 Infrared (a) and red (b) normalised PPG signals obtained from patient number five. Adapted from (8).

Patient Six:

Patient number six was a 44 year old female patient who had a craniotomy for the clipping of a cerebral aneurysm. At the time signals were taken, she had a heart rate of 50 beats per minute, a blood pressure of 126/60 mmHg, mean arterial pressure of 82 mmHg. Her peripheral SpO_2 readings were 100% throughout the measurement period. Total recording time was 257 seconds. Both the red and infrared signals were of good quality and had good demarcation, with no interference for greater than 70% of the recording. A 30 second trace obtained from this patient is shown in Figure 3.12.

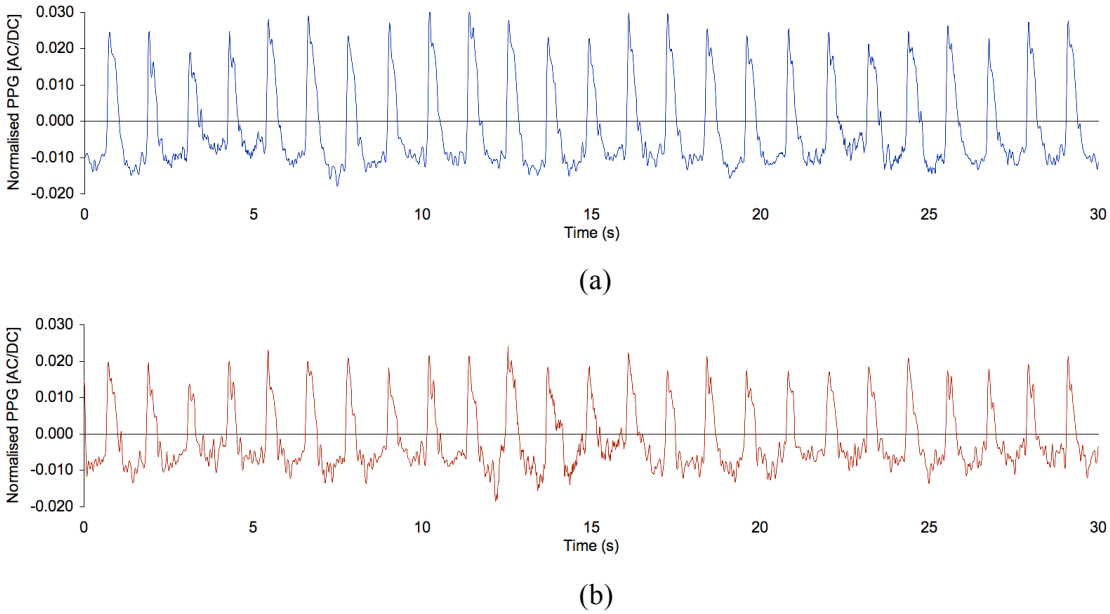


Figure 3.12 Infrared (a) and red (b) normalised PPG signals from patient number six. Adapted from (8).

The acquired red and infrared signals from all six patients were used to estimate the cerebral oxygen saturation of each patient. They were analysed retrospectively using 60-second samples of each waveform. This sample was chosen by visual inspection using the 'best' signal in terms of overall quality of the waveform. Waveforms with large amplitudes and minimal artefacts were selected. The arterial oxygen saturation was estimated from the cardiac-modulated components using a Fourier transforms algorithm for analysis. To summarise, the estimated values of oxygen saturation for each of the six patients are shown in Table 3.5.

Patient number	Estimated oxygen saturation (%)
1	98.2
2	100.5
3	94.8
4	90.4
5	52.0
6	92.6

Table 3.5 The estimated values of oxygen saturation in each of the six patients.

3.9.1 Discussion

This was a successful pilot study on the use of a specially built fibreoptic probe designed to measure PPG signals from brain tissue. These initial results are promising in that adequate signals were obtained from brain tissue. In addition, it confirmed the feasibility of using existing cranial bolts to house the fibres with no untoward effects.

In one of the patients (number three), this patient appeared to be more prone to ventilator artefacts in the signals obtained. This could be because the patient might have been relatively hypovolaemic, resulting in an exaggerated effect in blood pressure with mechanical ventilation. It could also have been due to individual sensitivity to mechanical motion from the ventilator.

It has to be noted, that relatively deoxygenated blood, absorbs red light more strongly than infrared light and any vessels with a transmitted pulse, including cerebral veins will give a large amplitude PPG signal. The implication that the blood is of low oxygen saturation may not always be due to arterial saturation readings but venous ones. The brain is enclosed in a fixed cavity and any fluid such as cerebrospinal fluid may contribute to pulsation in nearby large veins. Thus, the relatively low oxygen saturation reading in one of the patients (number five) could be due to the probe being in close contact with a large vein. Since it was not possible for us be sure where the cerebral vessels are in location to the burr hole once it is made, the placement of the bolt cannot be altered and readings could only be taken from that site. Thus the PPG signal could be influenced by any pulsatile vessel, and it would be difficult at this stage to distinguish between a vein or artery. This could have also been due to just differences in anatomical variation. This will need to be studied further, before any further comments can be made. The poor quality signals obtained from patient number four was attributed to the possibility that the fibres were not in the correct position i.e. one fibre was in further than the other, leading to a poor signal. There were no complications associated with insertion of the probe in all the patients studied. There was no bleeding, no attributable deleterious neurological sequelae such as seizures, or neurological deficits or any associated signs of infection.

3.9.2 Conclusions

This proof of concept study showed that that satisfactory quality red and near-infrared PPG signals could be obtained directly from human brain tissue with a fibreoptic probe, using the cranial bolt as a conduit for the fibres. The results of this study are certainly encouraging, and it would be interesting to see whether this method could yield similarly good results over a prolonged period of monitoring in the long term. Indeed further research and comparisons to other techniques currently available such as near-infrared spectroscopy may be warranted.

3.10 Measurement of brain oxygen saturation on the intensive care unit

In patients suffering from head injuries, secondary brain damage caused by neuronal lack of oxygen and blood supply is a common and potentially preventable cause of mortality and residual disability. By monitoring the pulse waveform and cerebral oxygen saturation, it may be possible to alert the clinician to changes in the clinical condition of the patient allowing appropriate therapy to be given with a view to improving patient outcome. Near infrared spectroscopy (NIRS) is currently used to monitor adequacy of cerebral perfusion by estimating oxygen saturation. Although this has the advantage of being a non-invasive technique, it has been suggested that the accuracy of NIRS is compromised by attenuation and modulation of light by superficial tissues e.g. skull, scalp. (8) Electrochemical oxygen sensors are also used transcranially in severe head injury cases. These systems have the disadvantage of requiring calibration prior to insertion, need to stabilise and respond (can take up to two hours to achieve stability), and are prone to inaccuracies caused by small haemorrhages around the sensor.

From the results obtained in the previous six patients, we concluded that we could obtain good quality PPG signals from brain tissue. We thus used the knowledge gained to obtain signals from brain tissue of a patient on the ITU at The Royal London who was in need of an intracranial bolt and ICP monitoring whilst recovering postoperatively on the unit.

We proceeded with a separate clinical study in a different clinical setting, which had full ethics committee approval. The primary aim of this study was to see whether we could obtain clinically meaningful signals for a prolonged period and to compare this with oxygen saturation values obtained from haemoximetry as well as the Near-Infrared Spectroscopy (NIRS). A secondary aim of this study was to see if any changes in ICP measurements correlated in anyway to PPG signals obtained.

3.10.1 Materials and methods

The triple channel IM-3 cranial access bolt used in the first clinical study on elective neurosurgical patients is also readily available for use in ITU patients, specifically those on the ITU at The Royal London Hospital. Currently, the bolt is designed to accommodate three sensors, one for ICP monitoring, one for Licox oxygen tissue sensor measurements and the last for temperature monitoring. In practice, at the ITU in The Royal London Hospital, only the ICP monitoring channel is used, thus, there were two other free channels for the insertion of the optical fibres for purposes of this study. The cranial bolt is designed to remain in place for several days, allowing the continuous monitoring of ICP in critically ill head injury patients. The IM-3 cranial bolt comes in a sterile packaging and is inserted usually in the operating theatre under fully sterile conditions. It is inserted under direct vision, by the neurosurgeons, after the formation of a burr hole in the scalp, and screwed in so that it sits tightly and securely. The fibres can then be passed through the lumens to rest directly on brain tissue. After analysis from the previous study, it was decided that the fibres would rest no more than 4 mm onto the brain tissue, to provide the best conditions for obtaining long-term readings using a minimally invasive technique.

In this study, a modification was made to the measurement system, in order to improve accuracy. A third light source close to the isobestic wavelength of 805 nm was added. This wavelength is the isobestic point for oxy and deoxy-haemoglobin, i.e. the wavelength at which the two haemoglobins have the same absorption of light. Any changes in the oxygen saturation of the blood would have minimal effect on any backscattering of light. As the only readily available LED was one with a wavelength of 810 nm, this was used instead.

In order to incorporate three light sources from one fibre to obtain measurements from three wavelengths of light, the three light sources had to be channelled into one single fibre. In the previous study, for the two lights sources, a commercially available Y-coupler was used (i.e. a bifurcated optical fibre). There was no commercially available coupler for three light sources, so this was custom made by our biomedical engineering group. A trifurcated fibre was made consisting of three short optical fibres of 400 μm in core diameter, joined to single larger fibre of 800 μm in core diameter which terminated at the distal end with an SMA connector. All fibres were threaded into a metal tube, optical adhesive applied to the un-terminated ends of the fibres and the entire construction supported by the application of strong PVC tape. The original infrared wavelength of 850 nm was also substituted for a light source with a wavelength of 940 nm as it was felt that 850 nm was too close to the wavelength of 810 nm to add any further value to the measurements.

3.10.2 Patient recruitment

The patient recruited was a 78 year-old female who was on the ITU at The Royal London Hospital for intensive care support following evacuation of an intracerebral haematoma in the frontal-temporal region. This patient initially presented to hospital with a GCS score of 3. She was a known hypertensive with a resting blood pressure of 165/64 mmHg. The patient had an urgent CT scan of her brain that showed the extent of the intracerebral haematoma and the need for urgent surgical intervention. The patient was taken to theatre to have a craniotomy to evacuate a haematoma and subsequently was kept temporarily sedated on a ventilator whilst recovering. As part of routine monitoring, an ICP bolt was inserted into the skull of the patient in theatres, so that ICP pressures could be monitored in the patient whilst on the ITU. Assent was obtained from the patient's next of kin. The fibreoptic probe was inserted into the spare ports on the cranial access bolt in order to record PPG signals. This occurred after about 20 hours from the initial time of presentation of the patient to hospital. The probe was placed approximately 4 mm into the region of the right frontal lobe and signals were recorded for a total period of six hours.

As part of routine ITU monitoring, the patient had continuous monitoring with a commercial peripheral (finger) pulse oximeter as well as an indwelling arterial line- allowing regular measurements of blood gases including blood oxygen saturation using a haemoximeter. The patient was sedated with propofol, an intravenous anaesthetic, intubated and lungs mechanically ventilated throughout the six-hour monitoring period with the fibreoptic probe. In addition a pair of NIRS sensors (Somanetics Corporation, Troy, MI, USA) was placed on the patient's forehead as per manufacturer's instructions and readings were taken at intervals from the NIRS monitor. The readings were taken over a six-hour period. During this time, the arterial oxygen saturation (SpO_2) from the commercial pulse oximeter was recorded manually and the arterial oxygen saturation (SaO_2) was measured from samples taken from the arterial line using a haemoximeter. In total, 54 pulse oximetry measurements and five haemoximeter measurements were recorded during the six-hour period. After about six hours, the patient started to move and wake up so the probe was removed and the monitoring discontinued. The patient was on the ITU for several days, and made a satisfactory recovery.

3.11 Results

In the first pilot study, the measurements were made over short time periods in the region of minutes. The average value for oxygen saturation was calculated for each patient using a single Fourier transform of fixed length. In this study, the signals were recorded over a period of hours, and the calculations made some time after the signals were acquired. The data was analysed by breaking the data down into a series of sets of one-minute in duration and a pair of discrete Fourier transforms applied to each set; one for each of the infrared and red channels respectively. Each pair of Fourier transforms was used to generate estimations of oxygen saturations from the peaks occurring at the cardiac ($SfcO_2$) and respiratory ($SfrO_2$) frequencies. Estimates were also made of the heart and respiratory rates from each data set. The data was analysed using specifically tailored LabVIEW VI programme. This analyses the data after the upper and lower limits of the cardiac or respiratory frequencies are manually entered. When the programme is run, red and infrared signals are recorded from the spreadsheet file. The main body of LabVIEW VI is contained within a loop, each time a loop runs, one-minute data sets are selected from the data in sequence. As the

sets are contiguous, 60 sets of data are obtained for each hour of recording, and fed into the 'amplitude spectrum' functions which produce two discrete Fourier transforms, in the form of one-dimensional numeric arrays. A sub-set of each spectrum (sub-spectral array) is produced which consists the part of each spectrum with either the cardiac or respiratory peaks. An array of red and infrared peak sizes is generated and saved to a spreadsheet file. The continuous oxygen saturations for 'cardiac' and 'respiratory' cerebral oxygen saturations, $SfcO_2$ and $SfrO_2$, were estimated from the acquired DC signals. The values of $SfcO_2$ were compared to a commercial finger pulse oximeter. A paired Student's t-test was used to see if there was any significant difference between the two. (88)(87)

In order to calculate the arterial oxygen saturation, the ratio of ratios (89) is averaged over a finite period consisting of *n* cardiac cycles. The mean value of (88) is used to estimate the arterial oxygen saturation (SpO_2) according to the Equation (3.2) below(4):

$$ScO_2 = 110 - 25\bar{R}_R \qquad (3.2)$$

The signals from the ITU patient were successfully recorded over the monitoring period. The total time period of monitoring was 353 minutes.

Figure 3.13 shows a 20-second sample of the normalised PPG signals obtained from the patient. It can be seen that both the red (660 nm) and infrared (940 nm) signals are fairly consistent in amplitude and consistency. There is some degree of modulation of the waveform consistent with frequencies in the respiratory range, but not to the extent seen in the first study on the intra-operative neurosurgical patients.

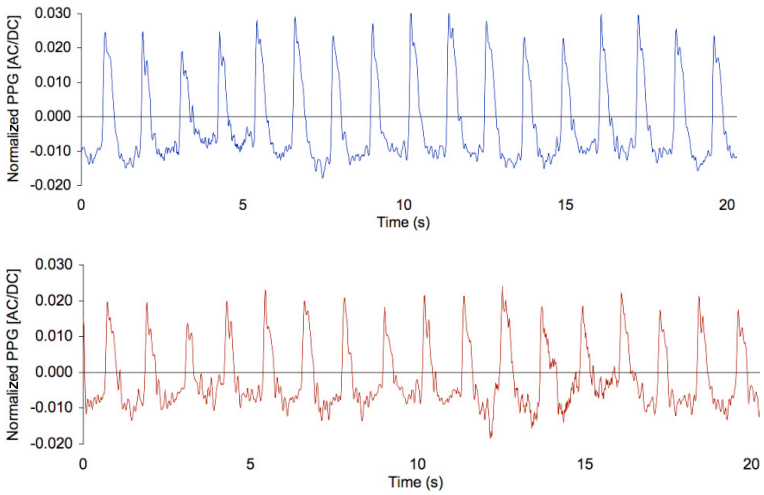


Figure 3.13 Sample of PPG signals obtained from patient number six. The first trace shows the infrared signals; the second trace the red signals. Adapted from (33).

During the six-hour measurement period, the $SfcO_2$ was significantly lower than the finger SpO_2 (P<0.001) and the blood SaO_2 (P<0.001) as confirmed by paired Student's *t*-tests. A steady trend of decreasing $SfcO_2$ was seen for the first four hours followed by a gradual rise. The mean (±SD) difference between $SfcO_2$ and finger SpO_2 (in saturation units) was -7.47(±3.4)% n=54. The mean (±SD) difference between $SfcO_2$ and blood SaO_2 was -7.37(±2.8)% n=5.

In terms of difference between that obtained from the calculated mean cardiac versus respiratory frequencies $SfcO_2$ and $SfrO_2$, in saturation units, was 15.4 ±(6.04)%. A paired Student's t-test on all the one-minute sets of data showed that the values of $SfrO_2$ were significantly lower than those of $SfcO_2$ (P<0.001).

Heart rate from the commercial ECG monitor (GE Healthcare Clinical Systems, WI, USA) was also compared to the trace obtained by the fibreoptic probe. The mean (±SD) difference between the heart rate obtained by the fibreoptic probe and the commercial ECG monitor was -2.31(±11.6) min^{-1}, n=46. There was thus good correlation during most of the monitoring period between the two.

Overall, there were just two periods in the whole period of monitoring when the photodetector output was abnormally low, and in both cases were associated with movement of the patient's head, and the fibres just needed to be re-positioned in order to rectify this.

3.11.1 Comparison with ICP

Throughout the monitoring period, ICP values were within normal limits i.e. less than 20mm Hg. Whilst there was a gradual decrease in the first four hours of the monitoring period, as the sedation was lightened, the patient began to wake up and move, with an increase in mean arterial pressure (MAP) as well as ICP towards the end of the monitoring period. The readings in $SfcO_2$ were observed to be similar to the pattern seen with the changes in ICP. The other variable which could affect ICP readings was the end tidal CO_2 (Et CO_2) which remained within normal limits, but did decrease slightly during the period of monitoring.

One of the reasons for adding the third wavelength of light (810 nm) was to allow for the calculation, using the Beer Lambert's Law, of changes in cerebral blood volume (CBV). Cerebral blood volume is a major factor in the regulation of cerebral haemodynamics. Any increase in cerebral blood volume is associated with the dilatation of pial vessels (the vessels that transport substances from cerebrospinal fluid to blood) and a rise in intracranial pressure. This in turn causes a decrease in cerebral perfusion pressure. This may in itself lead to a reduction of vasodilatory capacity or in practice a reduction of cerebral blood flow (CBF). Combined measurements of CBF and CBV allows for the calculation of the CBF/CBV ratio. This ratio can give an indication of local cerebral perfusion pressure (CPP). CBF and hence CPP is autoregulated in the normal brain and is governed by the Equation (3.3):

$$CPP = MAP - ICP \text{ (and sagittal sinus pressure)} \quad (3.3)$$

Where MAP = Mean arterial pressure: 1/3(systolic pressure - diastolic pressure) + diastolic pressure. In the normal brain, intracranial pressure and sagittal sinus pressure are negligible compared to systemic arterial pressure, and CPP is roughly equivalent to MAP. Cerebral blood flow is governed by the Equation (3.4) below:

$$CBF = CPP/CVR \quad (3.4)$$

where CBF is the cerebral blood flow and CVR is the cerebral vascular resistance

Thus, autoregulation is governed by changes in CVR. According to the Hagen-Poiseuille equation, which governs the flow of Newtonian fluids in tubes, an estimation of the factors that govern cerebral vascular resistance can be made. This suggests that the resistance is inversely proportional to blood viscosity and the fourth power of the radius of the vessel. Any decrease in cerebral perfusion pressure automatically causes a dilatation of precapillary resistance vessels, and any increase produces constriction. The average hemispheric cerebral blood flow is maintained at a fairly constant level, near 50 ml/100 g per minute in the adult human brain at rest by adjustments in the diameter of these cerebral resistance vessels.

There are three main theories behind the way autoregulation is controlled, namely: the myogenic, neurogenic and metabolic mechanisms of autoregulation.

a) myogenic theory: reflex changes in the tone of arteriolar smooth muscle are elicited by changes in transmural pressure. This is based on work done by Bayliss (1902). According to this theory, an increase in the transluminal pressure leads to stretching of smooth muscle within the vessel wall. Reflex contraction of radial fibres then results in constriction of vessel diameter. An opposite effect is seen with a decrease in transluminal pressure. (84)(90)

b) neurogenic theory: nerve fibres are known to exist around the cerebral vessels. The pial vasculature is richly supplied by noradrenergic sympathetic nerve fibres which originate mainly from the superior cervical ganglion. These fibres accompany the arteries and arterioles as they penetrate into and are distributed by the brain parenchyma. There is also increasing evidence for a serotonergic innervation originating from the raphe nucleus. It is also thought the substances such as EDRF (endothelium derived relaxing factor) is a factor in relaxation of the cerebral vasculature.

c) metabolic theory: a change in cerebral blood flow initiated by a change in perfusion pressure leads to a change in the local concentration of vasoactive substances normally eliminated by the bloodstream. This shift in concentration would affect the vascular smooth muscle in the direction of an auto-regulatory response. Factors such as CO_2, pH and O_2 were likely contributors to the metabolic regulatory response.

Thus several theories exist as to exactly how cerebral blood flow is autoregulated. However, pathological conditions such as an intracerebral tumour, aneurysm or any insult to the brain secondary to trauma, can and does disrupt the regulation of cerebral blood flow and brain metabolism.

3.12 Discussion

These results demonstrated that good quality three-wavelength signals could be successfully obtained from the brain tissue over a prolonged period of time. The monitoring period was only terminated as the patient was waking up. There were no technical failures or major problems with the system as a whole. The probe also fitted nicely down the port of the existing triple lumen system.

A possible reason why the oxygen saturation $SfcO_2$ was significantly lower than SpO_2 measured by the commercial pulse oximeter could be attributed to venous pulsation as opposed to arterial pulsation being detected by the probe. There was also similarity observed between $SfcO_2$ and ICP readings in terms of a positive correlation. During an increase in ICP, venous pulsation may be impeded resulting in a truer reading from the $SfcO_2$ compared to actual arterial values. Another factor which might have affected readings was the overall volume status of the patient. Central venous pressure readings were not noted. However, as blood loss was minimal for the surgery and blood gas results indicated good gas exchange, and that the patient was on intravenous fluid therapy for the duration of the operation, it could be assumed that she was adequately filled. The estimated changes in cerebral blood volume was negligible for the first half of the monitoring period, as one might expect for a patient that was sedated and ventilated, and then rose as the patient started to wake up.

The NIRS monitor was attached to this patient for part of the period of monitoring. NIRS monitors give a global indication of oxygen saturation of a specific volume of blood: mixed venous, arterial and capillary blood. However as the NIRS monitor measures global oxygen saturation (i.e. may not necessarily reflect any changes in overall oxygen saturation), it needed to be compared to estimated mixed venous saturation (SmO_2) in the brain in order to make any true comparisons. In order to

make any estimation of global oxygen saturation of the brain, calculation of cerebral blood volume would be needed along with computer modelling and simulation in order to provide a rough estimate. As there is no "gold standard" to compare cerebral arterial as well as venous saturations against, this leaves it difficult to make any true interpretations on the limited NIRS readings taken from the one patient.

3.13 Conclusions

The primary aim was to see whether viable PPG signals could be obtained from the human brain. The initial pilot study showed this to be possible. This allowed us to continue with using the probe to acquire PPG signals over a longer period on the ITU in patients who required an ICP bolt for their head pathology.

There was, however, only one patient studied on the ITU, making it difficult to comment further on its use in this setting. However, the results obtained were promising with no untoward side effects in the patient studied. The reason behind the lack of recruitment of more patients was because the hospital's own sterilisation service was closed during the intended period of study recruitment, and as a result of the regulations and restrictions imposed by the substituted outsourced company, we were unable to arrange for sterilisation of the fibres. Essentially, their management was unwilling to accommodate sterilisation of the fibres for purposes of the research study, despite reassurances and documented, evidence-based confirmation of both their suitability and regular use for biomedical use. Despite this, the feasibility of using this probe as a way of monitoring the brain over a prolonged period of time remains a possibility and justifies performing more research using this probe.

CHAPTER FOUR–MEASUREMENT OF OXYGEN SATURATION VIA THE OESOPHAGUS

4.1 Introduction

In chapter three it was stated that pulse oximetry is part of routine monitoring in anaesthesia and intensive care medicine. In fact, in the 1980s, it became a mandatory standard for monitoring during anaesthesia. It is also widely available in many other clinical settings, and used as part of routine care on many hospital wards and clinical areas. Although pulse oximeters generally produce reliable signals and is widely available in most clinical settings, there are significant limitations on the accuracy and availability of pulse oximeter data in some circumstances. Ironically, the use of conventional pulse oximetry in those groups of patients where continuous monitoring of oxygenation status would be most beneficial, their physiological condition can lead to errors or discrepancies in measurements.

When peripheral perfusion is poor, as in states of hypovolaemia, hypothermia, vasoconstriction, low cardiac output states and states of low mean arterial pressure; oxygenation readings become extremely unreliable or cease altogether. There are also certain groups of patients, such as those who have suffered extensive burns and/or damage to skin and extremities, in whom the use of pulse oximetry can be extremely limited and inaccurate. As such, the need for a good pulse waveform trace is almost unobtainable in such cases. Under these conditions, some pulse oximeters give a blank screen on the display or give a message such as ‘low quality signal’ or ‘inadequate’ signal or simply a poor trace. Thus, the presence of a functioning pulse oximeter should not be construed as evidence of adequate tissue oxygenation or oxygen delivery to vital organs.

To overcome the inherent limitations of current commercial pulse oximeters where peripheral perfusion is compromised, Kyriacou et al of the Biomedical Engineering Research Group at City University, developed an innovative oesophageal probe, that allowed pulse oximetry measurements to be evaluated in anaesthetised patients. (89) (90) In the evaluation of their probe, they successfully demonstrated that measurable PPG signals and SpO_2 values could be detected in the oesophagus of healthy patients

during anaesthesia and from patients undergoing cardiothoracic surgery. A further development was the design of a fibreoptic probe that could measure clinically meaningful PPG signals from various sites, including the oesophagus and other cavities such as the intra-abdominal cavity.

The limitations of current commercial pulse oximetry technology were previously discussed. The need for commercial pulse oximeters to be attached to the peripheral parts of the body is the reason for one of its major limitations: the need for an accessible peripheral pulse/perfusion so that it can be used accurately to obtain any readings. The problem with this is pulsatile flow can be easily impeded in certain situations and considerably negates its use in certain population groups for example patients with severe burns or those whose perfusion is poor due to vascular disease or who are hypothermic. In addition, the need to use certain classes of drugs, in high risk patients undergoing major surgery, such as adrenaline or noradrenaline, can cause significant vasoconstriction in the periphery and hence inaccuracies when pulse oximetry is in use. It can be argued that this is probably the group of patients who need to have their oxygen saturation monitored most closely and yet are unable to, due to the limitations of the commercially available pulse oximeter.

One possible way of overcoming the problem of being able to accurately measure oxygen saturation in states of poor peripheral perfusion, is to try and obtain those measurements from internal sites in the human body, one such site being the oesophagus. The oesophagus itself is a fairly straight muscular tube (roughly 23 to 25 cm long) that extends from the pharynx to the stomach and signifies the start of the human alimentary tract. It follows the curve of the vertebral column as it descends through the neck and posterior mediastinum. The oesophagus begins in the midline at the level of the lower cricoid border (C6). It then moves to the left side of the neck before returning to the midline at T5. It then extends to the gastric cardia at T7. At the level of T10, it passes through the oesophageal hiatus at the level of the diaphragm. It ends at the level of T11 at the gastric cardiac orifice. In the upper 1/3, the wall is formed from striated muscle, the middle 1/3 is formed of mixed smooth and striated muscle whilst the lower 1/3 is formed of smooth muscle. At the inferior end lies the oesophagogastric junction where the oesophageal sphincter acts as a physiological means of preventing gastric reflux.

Anatomically it is divided into three parts: cervical, thoracic and abdominal which follows its blood supply. The cervical part is supplied by branches of the inferior thyroid artery, the thoracic part by branches of the descending aorta and bronchial arteries and the abdominal part by branches of the left gastric and inferior phrenic artery. The venous drainage is similarly divided. The cervical part is drained by the inferior thyroid veins, the thoracic by the azygos, hemiazygos and accessory azygos veins and the abdominal part by the abdominal azygos and left gastric vein. Since the left gastric vein is a tributary of the portal vein (forming a portal-systemic anastomosis), in portal obstruction, these veins may varicose and burst into the lower oesophagus causing a fatal bleed. (91)

The cervical part of the oesophagus is supplied by rami from the recurrent laryngeal nerves and cervical sympathetic trunks; the thoracic part is supplied by branches of the vagus, oesophageal and sympathetic trunks and greater splanchnic nerves. The abdominal part is supplied by the vagal and thoracic sympathetic trunks, the greater and lesser splanchnic nerves and the plexuses of the left gastric and inferior phrenic arteries. The lymph drainage is to the deep cervical, posterior mediastinal and left gastric nodes which lead onto the coeliac nodes and eventually the thoracic duct.

Kyriacou et al. described a reflectance oesophageal pulse oximetry system which consisted of a oesophageal probe comprised of two infrared and two red LEDs (of peak emission 880 nm and 655 nm respectively) arranged adjacent to a photodetector and was designed to fit into a size 20 French gauge plastic transparent disposable naso-gastric tube. (92) In a clinical trial of the system by Kyriacou et al, the oesophageal probe was used and compared with the peripheral pulse oximeter (SpO_2) in 49 patients undergoing hypothermic cardiothoracic bypass surgery. Photoplethysmographic signals were observed at various depths in the oesophagus and oesophageal SpO_2 values were compared with those measured using a commercial finger pulse oximeter. Measurable PPG traces at red and infrared wavelengths were obtained in the oesophagus in all of the 49 patients. (93) In their study, they also found that in five out of the 49 patients, there were one or more episodes of at least ten consecutive minutes whereby the commercial finger pulse oximeter failed to display any PPG signals and give any readings of oxygen saturation. Vasoconstriction and low cardiac output states impede peripheral

perfusion and make the detection of any pulsatile signal low to negligible. In contrast at these stages, the oesophageal pulse oximeter functioned well throughout those periods. Thus, although pulse oximetry is a well and widely established tool for monitoring oxygen saturation, there are cases where its use is limited and prone to issues of reliability and accuracy. (91)

Pulse oximetry allows continuous non-invasive monitoring of arterial blood oxygen saturation. Pulse oximeters estimate arterial blood oxygen saturation by shining light at two different wavelengths, red and infrared, through vascular tissue. The pulsatile component of the PPG signal is assumed to be due to the arterial blood component. The magnitude of the red and infrared signals are sensitive to changes in arterial oxygen saturation due to differences in light absorption of oxygenated and deoxygenated haemoglobin (Hb) at these two wavelengths. The ratios of these amplitudes and the corresponding non-pulsatile PPG components are used to estimate the arterial blood oxygen saturation (SpO_2). Thus the limitations of pulse oximetry are manifested in the fact that it relies on the presence of adequate peripheral arterial pulsations, which are detected as PPG signals. Therefore, pulse oximetry may not be accurate in patients who have poor peripheral perfusion i.e. hypothermic or where pulses are absent or where routine sites for placement of the oximeter is not available e.g. burns patients/limb amputees. There have been previous studies, which have looked at the use of a oesophageal pulse oximetry probe in burns and cardiothoracic patients with good result. (94)(92)

The PPG signal is a potentially valuable indicator of both oesophageal perfusion and also general well being. The use of optical fibres to transmit light to and from the tissue offers several advantages in sensing applications such as this. Firstly, they allow a degree of miniaturisation that is difficult to attain using conventional sensors, allowing continuous measurement of oxygenation (or other variables) from remote parts of the body. Mounting the optoelectronic components outside the body reduces the risk of electric shock as fibres are typically constructed from glass or plastic (both electrical insulators). Similarly the risk of thermal injury is considerably less compared to the case of emitters placed in contact with tissue. Therefore a logical next step in this research was to develop a fibreoptic probe that could be used to measure oxygen arterial saturation in the oesophagus. There was much discussion

amongst myself and the engineers as to size and how the probe could be feasibly placed into patients with minimal or no untoward effects. It was decided that using a sealed nasogastric tube to encase the fibres would be a very safe and effective option, without compromising the potential quality of signals that could be obtained. In using the probe, the vascular anatomy of the oesophagus had to be taken into consideration. Thus, a relative contraindication to using it would be in patients with abnormal oesophageal pathology such as varices. With this in mind, a protocol was drafted, ethics approval obtained and patient recruitment began (see Appendix A).

4.2 Aims

The primary aim of this study was to be able to detect signals with this new probe whilst using the existing conduit of commonly used naso-gastric tubes available in all operating suites. The secondary aim was to analyse and compare results to traditional methods of finger pulse oximetry.

4.3 Materials and methods

An oesophageal probe was developed which comprised a cylindrical epoxy moulding in which two optical fibres were embedded as shown in Figure 4.1.

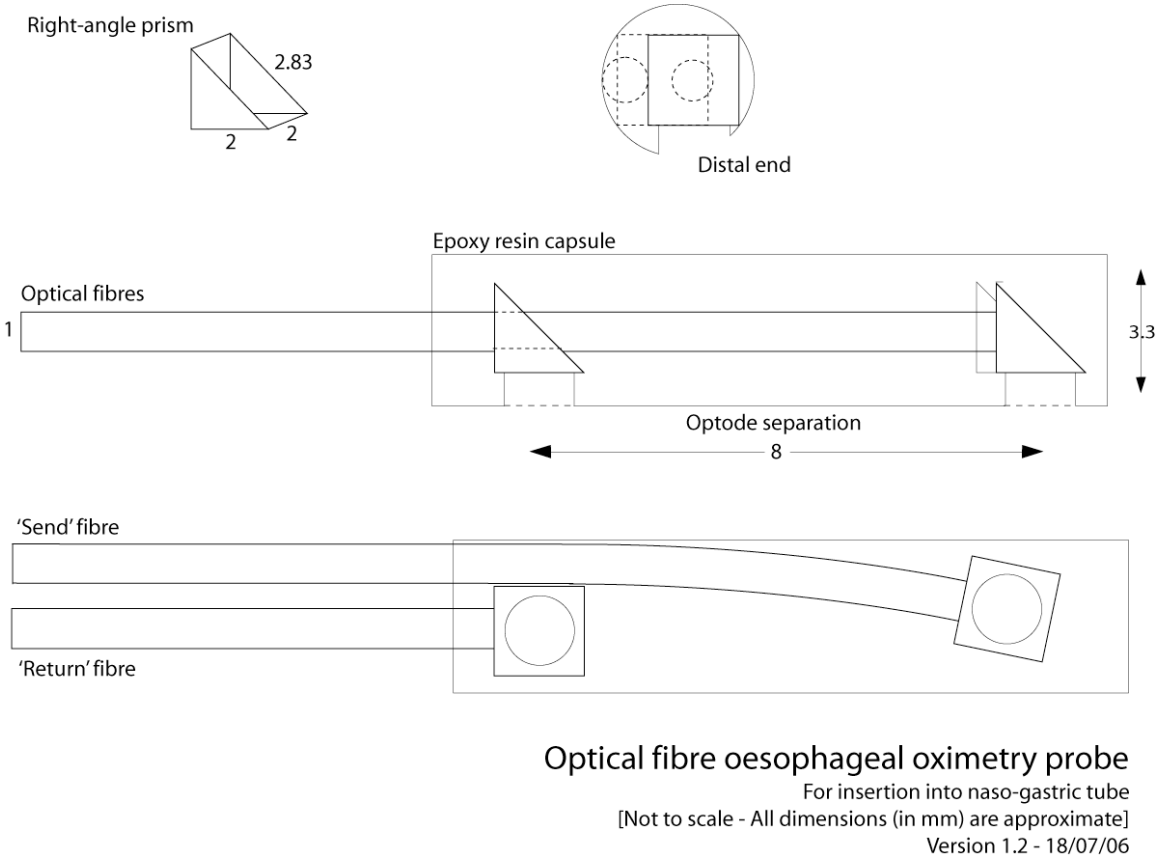


Figure 4.1 Schematic diagram of the oesophageal probe. Reproduced from (91).

These optical fibres had a larger core diameter of 600 μm (instead of 400 μm as used in the other studies) allowing the transmission of more light. The probe was inserted into a clean, sealed naso-gastric tube prior to insertion. The fibres used were approved for medical use and constructed from biocompatible materials. The naso-gastric tube has two perforations close to the distal end, which were blocked using a silicone bung prior to use (see Figure 4.2). The tube was also marked using a non-toxic sterile permanent marker at 5 cm intervals to enable accurate positioning in the oesophagus.

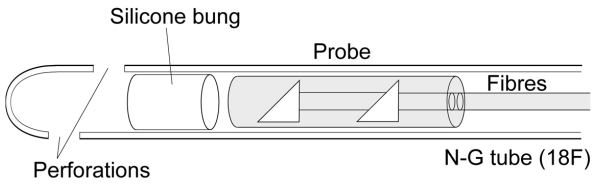


Figure 4.2 Schematic diagram of end of probe. Reproduced from (95).

The proximal end of the fibres are connected to a box containing two (red and infrared) light sources, a photodetector, power supplies (two 12 V lead acid batteries), a circuit board and a computer interface. A block diagram of the system is shown in Figure 4.3. The circuit board performs the following functions:

- switching the light sources on and off
- amplification of the detected light intensity signals
- filtering the signals to remove interference
- separation of pulsatile (ac) signals from non-pulsatile (dc) signals
- synchronisation of computer data acquisition with light source timing.

The instrument box is connected to a data acquisition card (National Instruments Inc., Austin, TX, USA) installed in the PCMCIA slot of a notebook computer.

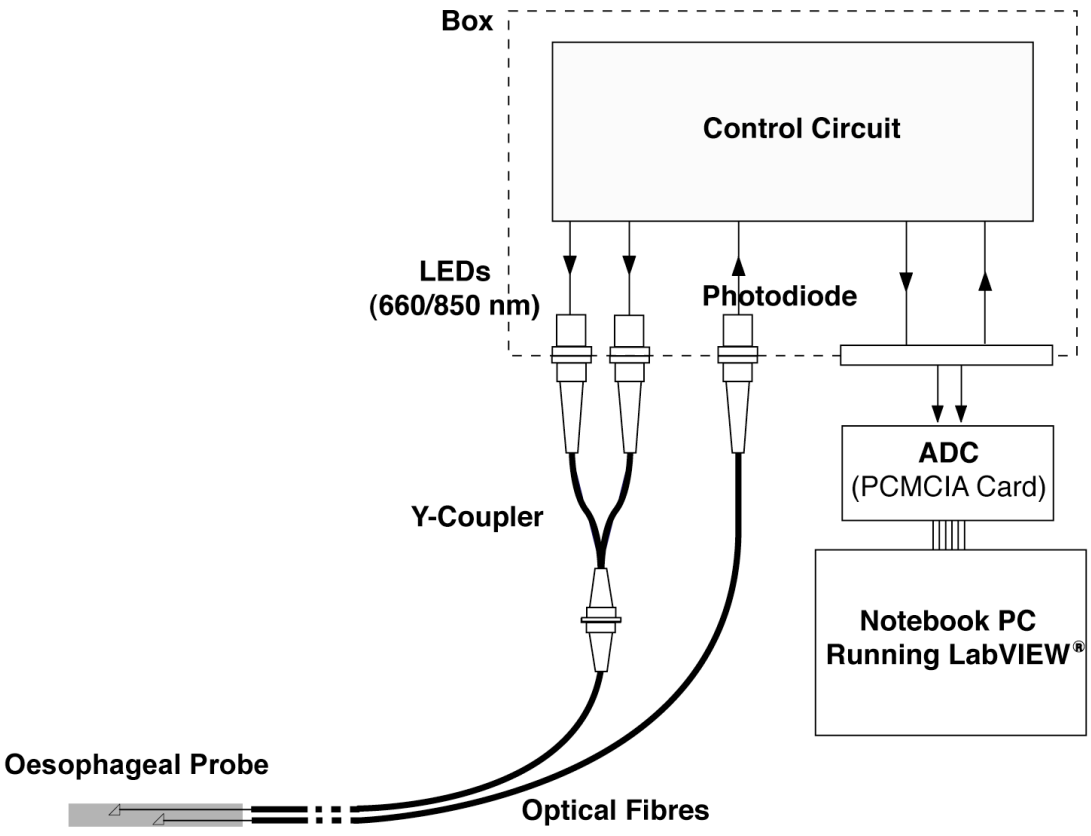


Figure 4.3 Block diagram of the measurement system. Adapted from (96).

We obtained approval from the Research Ethics Committee as well as the Medicines and Healthcare Products Regulatory Agency (MHRA) to study 20 patients using the probe. Patients undergoing minor general surgical procedures requiring tracheal intubation and mechanical ventilation were deemed suitable for this study. Adult patients aged (18 to 70) and classified as 'low risk' by the American Society of Anesthesiologists (ASA 1 to 3) were identified from the elective operating lists at Barts Health NHS Trust. Any patients in whom we anticipated difficulty with probe placement were excluded. Other patients that would be excluded were those of known difficult airway anatomy, any abnormality of the upper gastrointestinal tract, clotting disorders, history of oesophageal varices, hiatus hernia, any oesophageal pathology, previous gastric surgery, and pregnant women. After suitable patients were identified, full written informed consent was sought prior to their scheduled surgery.

After induction of anaesthesia and immediately after tracheal intubation, the probe contained within a sterile naso-gastric tube was inserted into the oesophagus by the anaesthetist, via the patient's mouth, under direct vision with a laryngoscope. The tip of the probe was placed at a depth of 35 cm in the oesophagus as measured from the front incisors. Once the probe was in position, the light sources were switched on and signals recorded for 100 seconds. The probe was then withdrawn 5 cm at a time and signals recorded for a further 100 seconds at each position until the probe was at a depth of 15 cm. The arterial oxygen saturation was measured using a commercial finger pulse oximeter (Datex-Ohmeda, Helsinki, Finland). The lungs were mechanically ventilated throughout this monitoring period. Peak airway pressures were recorded, as well as blood pressure readings during the measurement period. The probe was removed at the end of the measurement period, before the patient was moved from the anaesthetic room to the operating theatre, and surgery commenced. Each patient was reviewed post-operatively, with no documented adverse events.

4.4 Results

20 patients were recruited to the study. In all cases, the oesophageal probe passed easily into the oesophagus with no resistance and PPG signals obtained without any major issues. Signals were successfully obtained from 19 patients, with the one

failure attributable to poor signal quality. The patient demographics are shown below in Table 4.1.

Male:Female	7:13
Mean age (±SD)	43.3yrs (13.6)
Mean height (±SD)	167.4 cm (9.3)
Mean weight (±SD)	74.9kg (13.0)
Mean BMI (±SD)	26.7 (4.1)

Table 4.1 Patient demographics.

The PPG (AC signal) was separated from the total intensity (AC+DC) signal using filters incorporated into the measurement circuitry. The PPG signal was normalised by dividing the signal by the simultaneously recorded AC+DC signal. This has the effect of standardising the red and infrared signals levels, eliminating any differences in signal intensity caused by differences in brightness of the light sources, differences in sensitivity of the photodetctor to each wavelength and other effects. Also any slowly changing variations in any of these factors are eliminated. The peak-to-peak amplitudes of the normalised PPG signals were calculated for each heartbeat using a peak and valley detection algorithm incorporated into a LabVIEW virtual instrument.

Figure 4.4 below shows typical PPG waveforms obtained over a 30-second period at various depths.

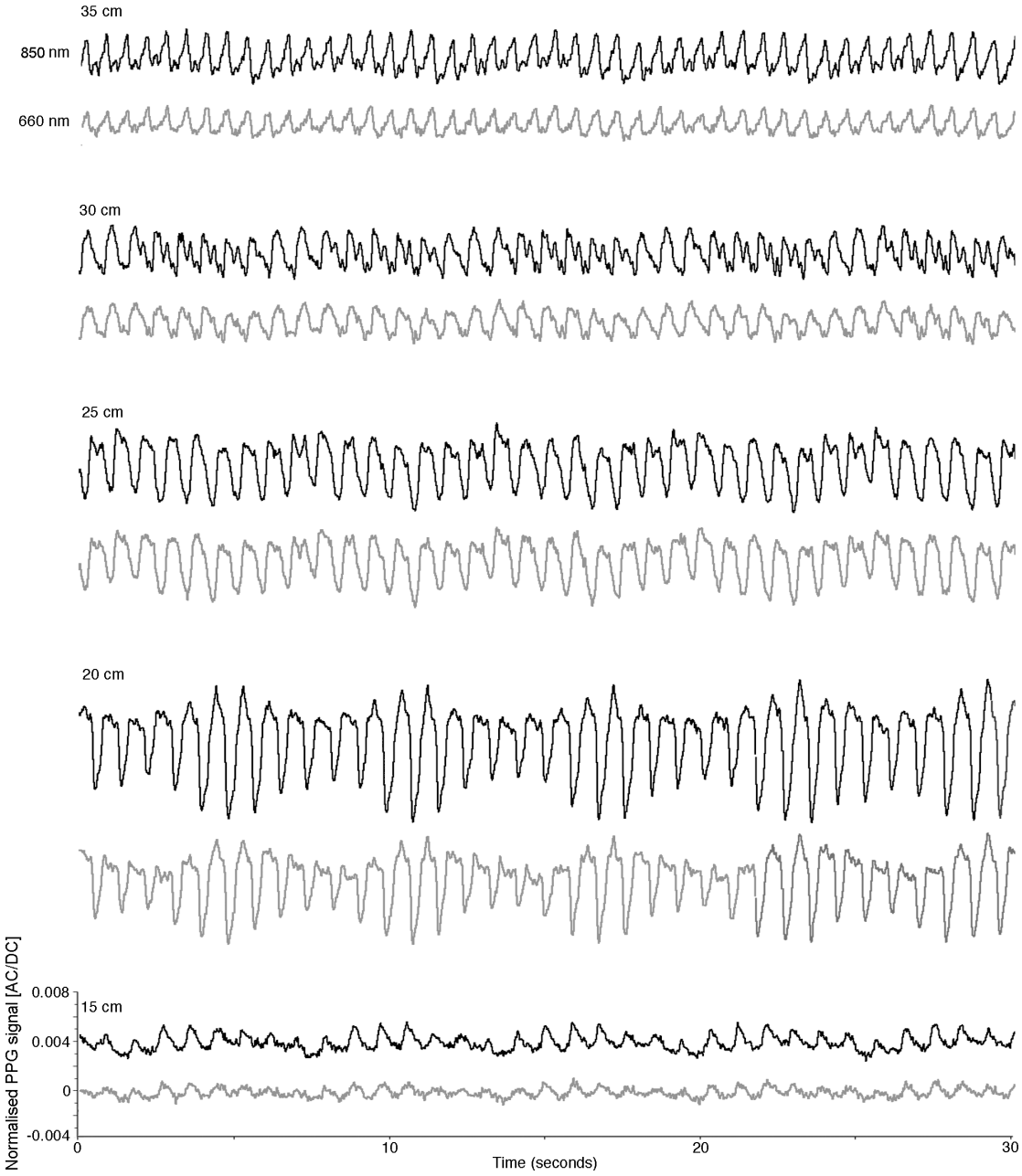


Figure 4.4 Showing 30-second samples of the normalised AC PPG waveforms obtained at each measurement depth. Reproduced from (96).

Figure 4.5 shows a bar graph of the mean (±SD) of the normalised AC PPG amplitudes at red and infrared wavelengths at the five monitoring depths for all patients. The AC signals in the mid to lower oesophagus (depths of 20 cm or greater) have significantly larger mean amplitudes at both wavelengths than those in the upper oesophagus (15 cm). The maximum mean oesophageal amplitude for each wavelength occurs at the depth of 20 cm.

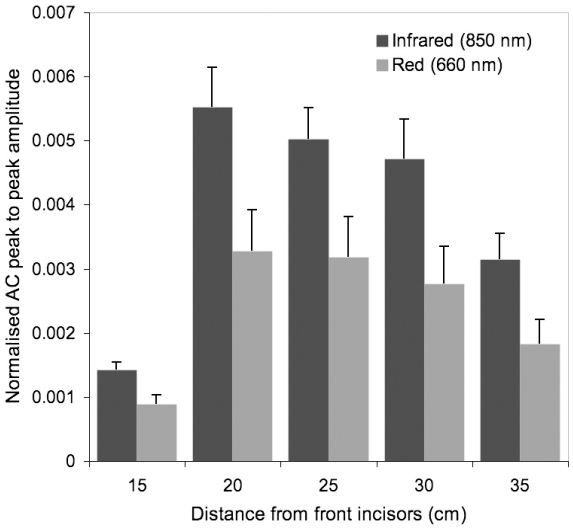


Figure 4.5 Bar graph of the mean (±SD) of the normalised AC PPG amplitudes at red and infrared wavelengths at the five monitoring depths for all patients. Reproduced from (96).

In this model, any movement of the probe, caused a change in amplitude of DC signal, with small amount of modulation from the respiratory frequency. There was significant change in amplitude of the AC signal with depth of the probe, especially at greater depths. The overall morphology of the PPG signal varied greatly with the depth of the probe.

The ratio of ratios was used to calculate the oesophageal arterial oxygen saturation (SoO_2), using the equation $SoO_2 = 110 - 25R_R$. The maximum mean amplitude for both wavelengths was at a depth of 20 cm. The amplitudes of the red and infrared normalised PPG signals obtained at 15 cm were significantly smaller ($P<0.001$) than those obtained at all other depths, using a paired Student's t-test. There was no significant difference between amplitudes at other adjacent depths (i.e. 20–25 cm, 25–30 cm and 30–35 cm).(96)

The mean red and infrared signals at each depth were calculated using the ratio of ratios. To compare the signals between the patients, the 'best depth' (i.e. depth at which signals were best for each individual patient) was chosen. The mean ratio of ratios for each patient was also calculated from the PPG amplitudes. Table 4.2 shows several variables derived from the signals for each patient obtained at what was the 'best depth'. From the results, there is quite a great degree of variability in the amplitudes of the variables.

Pat. #	'Best' depth (cm)	Normalized PPG amplitudes		Mean SoO_2 (%)
		Red ($/10^{-3}$)	Infrared ($/10^{-3}$)	
1	30	10.7	14.0	90.9
2	20	11.6	16.8	92.7
3	30	1.03	2.74	100.6
4	25	7.14	6.86	84.0
5	25	16.5	24.8	93.4
6	25	4.94	12.4	100.0
7	30	3.72	9.33	100.0
8	25	4.82	6.52	91.5
9	20	3.22	5.58	95.6
10	35	2.68	4.16	93.9
11	30	4.85	8.21	95.2
12	35	3.98	5.51	91.9
13	30	3.73	7.80	98.0
14	30	4.14	6.68	94.5
15	25	2.57	3.91	93.6
16	25	3.66	6.78	96.5
17	20	5.59	8.59	93.7
18	25	6.08	7.95	90.9
20	25	1.67	1.99	89.0

Table 4.2 Table of PPG signals obtained at the 'best depth'. Where SoO_2 is the oxygen saturation from the oesophageal probe. Adapted from (96).

The signals from the mid-oesophagus had the best signals. The mean value of oxygen saturation for all 19 patients was 94% (± 4.0%). The oxygen saturation recorded by the standard commercial pulse oximeter probe, was in the range of 98–100% in all 19 patients.

At the time of insertion of the oesophageal probe as well as when the measurements were recorded, blood pressure (BP) and peak airway pressures (PP) were also noted. Further analysis of the data taken from the 20 cm depths was performed, since this depth is favourable by virtue of the fact that for the group of patients as a whole, the greatest mean signal intensity was obtained at this depth. At this depth, the normalised PPG amplitude was plotted against arterial pulse pressure, mean arterial pressure (MAP), arterial systolic pressure, and arterial diastolic pressure. Figure 4.6 shows the graph of normalised PPG amplitude versus average arterial pulse pressure

over a five-minute period, the equation of the line was calculated by least squares regression giving a correlation coefficient 0.766. Similarly, Figure 4.7 shows the graph of normalised PPG amplitude versus mean arterial pressure, with a correlation coefficient of 0.504; Figure 4.8 shows the graph of normalised PPG amplitude versus arterial systolic pressure, with a correlation coefficient of 0.644; Figure 4.9 is the graph of normalised PPG amplitude versus arterial diastolic pressure, with a correlation coefficient of 0.292. From the four graphs, one can see that correlation is best when plotted against arterial pulse pressure (systolic minus diastolic pressure).

A Bland-Altman (96) comparison (Figure 4.10) was performed between oesophageal oxygen saturation (SoO_2) and oxygen saturation via finger pulse oximetry (SpO_2), measured at best depth. The horizontal lines show mean ±2SD, enclosing 95% of points. The lower the SoO_2, the bigger the negative difference in readings as finger oxygen saturation was always greater than 97%. Finally, the difference between SoO_2 and SpO_2 was also plotted against the average peak airway pressure in Figure 4.11. There is a general trend for subjects ventilated at higher peak airway pressures to exhibit lower oesophageal oxygen saturation values compared to those measured from the finger.

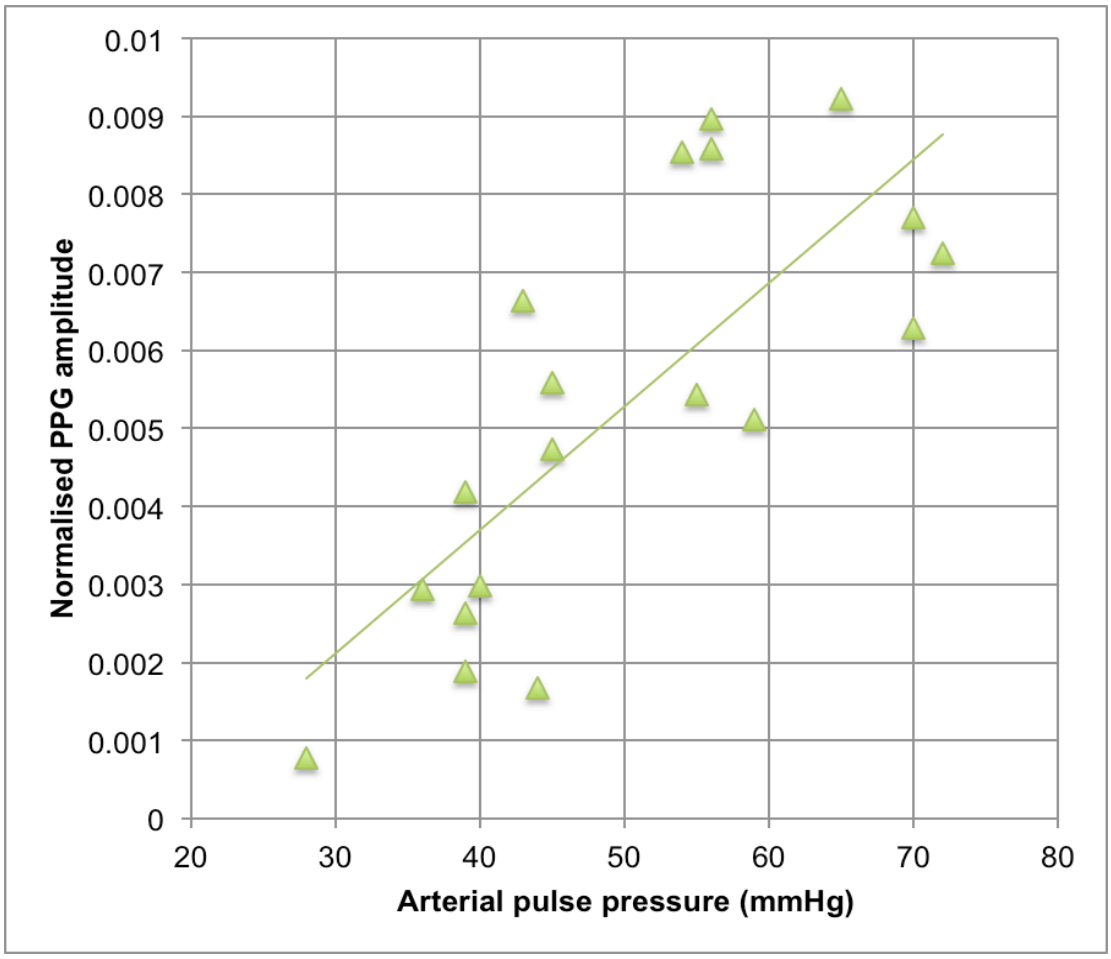


Figure 4.6 Plot of normalised PPG amplitude versus arterial pulse pressure; correlation coefficient 0.766.

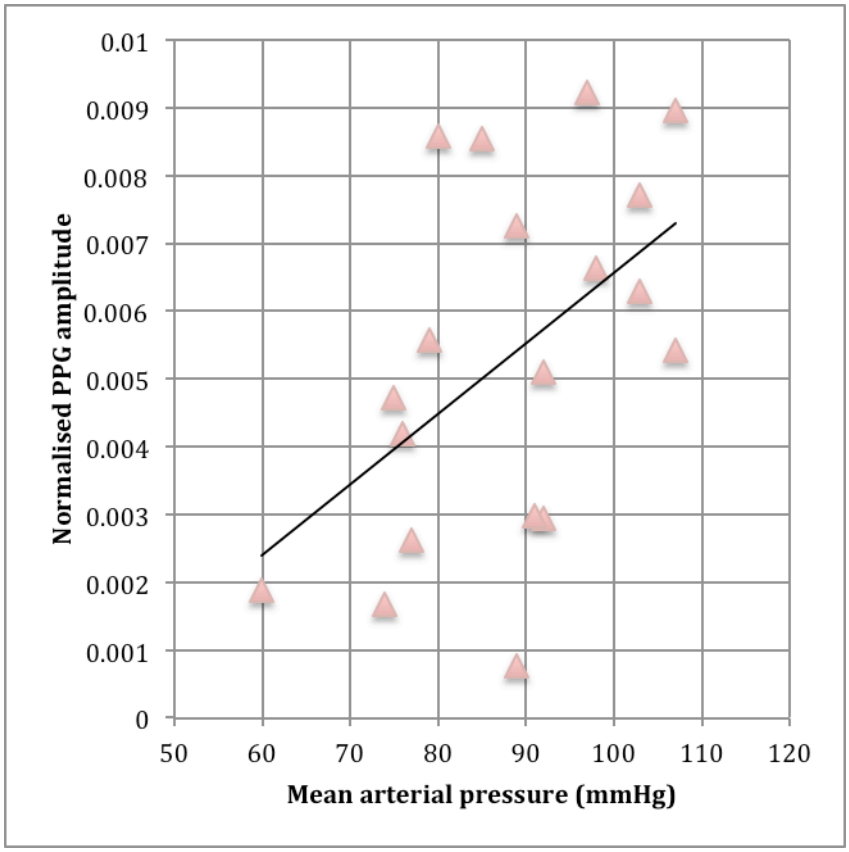


Figure 4.7 Plot of normalised PPG amplitude versus mean arterial pressure (MAP); correlation coefficient 0.504.

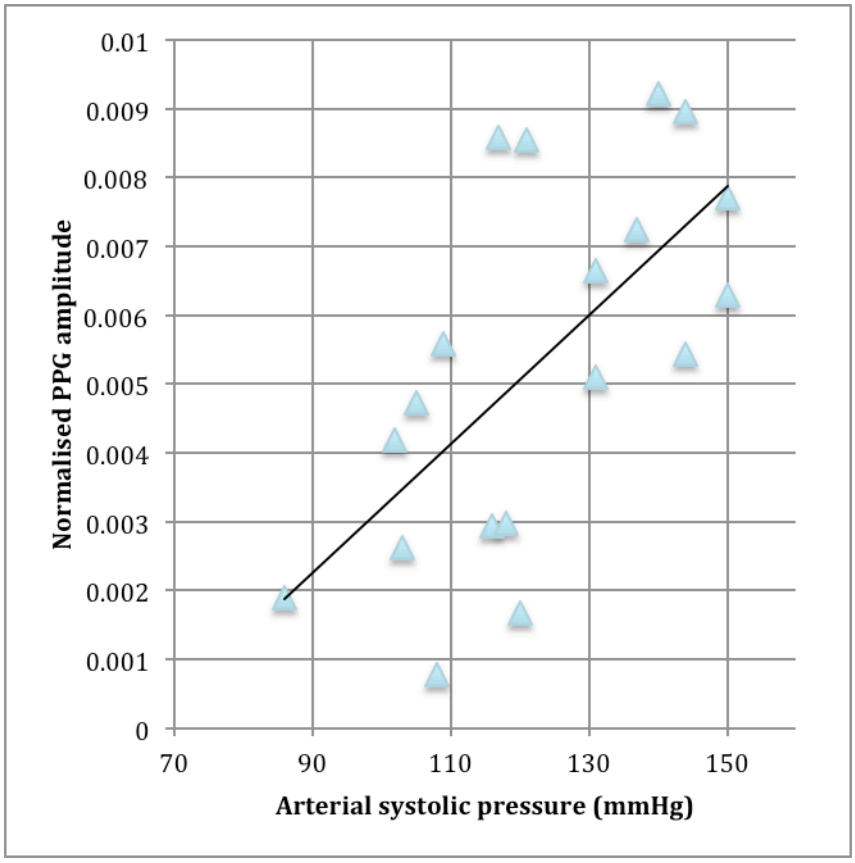


Figure 4.8 Plot of normalised PPG amplitude versus arterial systolic pressure; correlation coefficient 0.644.

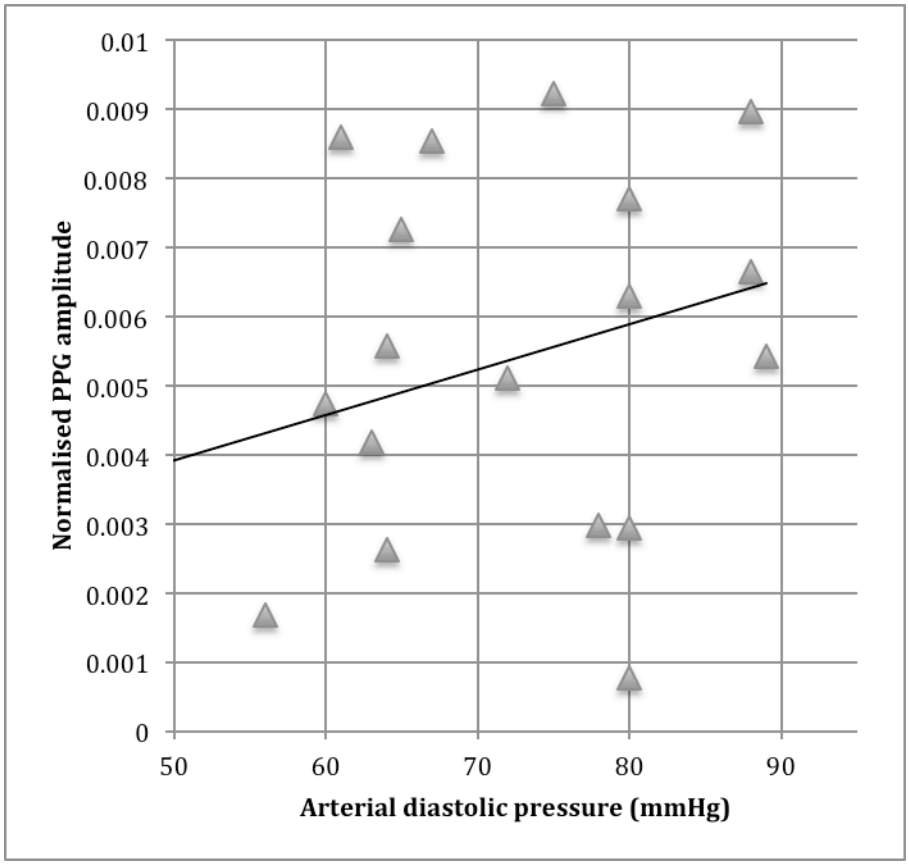


Figure 4.9 Plot of normalised PPG amplitude versus arterial diastolic pressure; correlation coefficient 0.292.

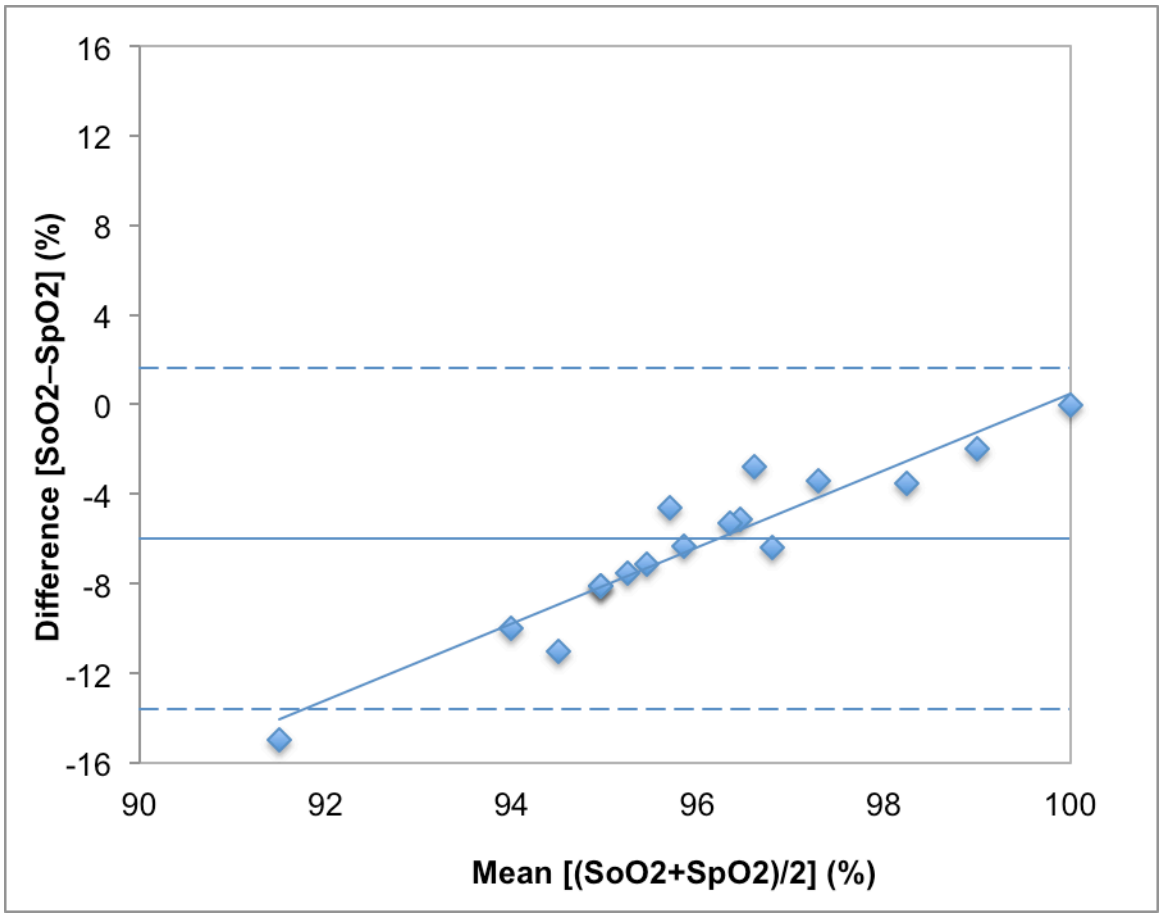


Figure 4.10 Bland-Altman comparison of oesophageal oxygen (SoO_2) and oxygen saturation readings (SpO_2).

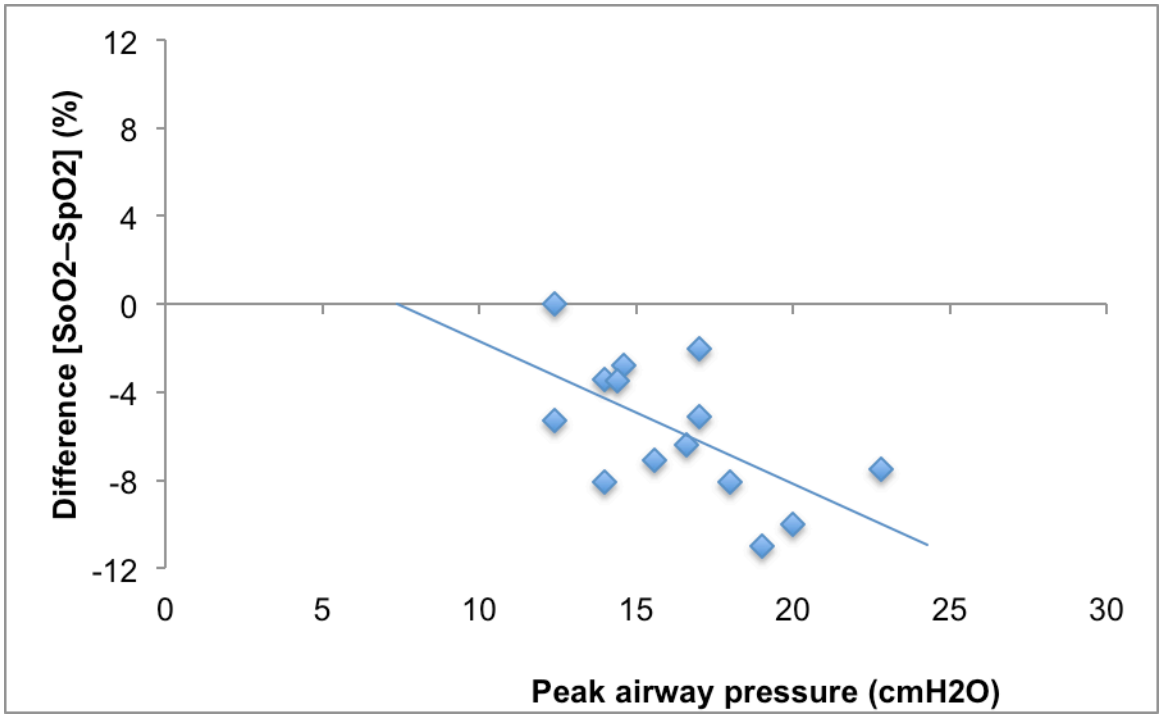


Figure 4.11 Graph showing the relationship between peak airway pressure and SoO_2, SpO_2 difference.

4.5 Discussion

This demonstrated that PPG signals could be reliably recorded from the oesophagus. The amplitude and quality of the signals depended on the depth of the probe. In this study, the greatest amplitude (i.e. best quality) signals were at about 20 to 30 cm from the teeth. In a different study by Kyriacou et al, using a non-fibre optic probe, they found similarly good readings at the same depth. One reason could be that at this depth, the locality of the descending aorta is in close proximity to the oesophagus and hence good amplitude PPG from this big pulsatile structure may have contributed to this.

In this study the value of the mean oxygen saturation of 94 ± 4.0% was lower than that recorded from the finger using the commercial pulse oximeter. The slight negative bias may be attributable to the use of an algorithim for calculation of the SpO_2 which was developed from experimental measurements using transmittance mode probes on a different measurement site (the finger rather than the oesophagus). There may also have been inaccuracies from mechanical ventilation with the probe in close proximity to the lungs and the heart. It has been observed that PPG signals are

sensitive to the movement of the tips of the fibres relative to the surface of tissues as well as movement of the fibres themselves. It may also be supposed that the induced movement modulation, would be similar in magnitude for both wavelengths, so the calculated ratio-of-ratios (normally <1 for arterial blood) would be higher in the case than with no movement. This would very likely result in underestimation of the measured oxygen saturation.

The graphs drawn in Figures 4.6 to 4.9 show that there is a possible correlation between the amplitude of signal obtained and blood pressure; in particular the correlation was strongest when compared against arterial pulse pressure (correlation coefficient of 0.766). This finding is not surprising as good PPG signals are dependent on adequate circulation and pulsatile blood flow. The differences between SoO_2 and SpO_2 measured at best depths against the mean of the two measurements (Bland-Altman plot) in Figure 4.10 showed small bias between the two methods and suggests that the oesophageal probe could be an accurate substitute for finger pulse oximetry. The graph shown in Figure 4.11 illustrated that airway pressure had an effect on PPG readings obtained. It showed that the higher the peak pressure in the airways the lower the readings obtained. This is not unexpected, as an increase in intrathoracic pressure would cause a decrease in blood flow temporarily in the thoracic part of the oesophagus and affecting blood flow, in particular venous compression within the oesophageal wall that occurs during the course of positive pressure ventilation. Furthermore, the volume of venous blood is likely to be affected by the airway pressure so periodic modulation of the venous blood would have an effect on the relative intensity of red and infrared light detected by the probe. This in turn could affect the calculated oxygen saturation value.

The principle underpinning pulse oximetry is the assumption that the 'pulsatile component' is solely comprised of the signal from blood in the arterial vasculature (i.e. the absorption increases as the path length increases during expansion of the arterial vessel), and that the venous component is static. In reality, this may not always be the case. Here we can see that venous blood is effectively confused with arterial blood due to its variable volume, plausibly leading to underestimation of the oesophageal oxygen saturation. This effect is greatest at high airway pressure as might well be expected.

The aim of seeing whether this innovative fibreoptic probe could be used to obtain useful signals was shown to be a success. However, in this study, we compared this to the finger pulse oximeter instead of measuring against arterial and venous blood oxygen saturations, as this was not deemed appropriate in this group of patients. Certainly from this pilot study, the results are promising and further clinical studies comparing against CO-oximetry would be warranted.

4.6 Conclusions

20 patients were recruited into this study with no untoward events. 19 results were deemed suitable for use in the final analysis. Good signals were obtained from 19 patients allowing comparison between values obtained from the fibreoptic probe with commercial pulse oximetry. There appeared to be a discrepancy in results by about 4% either way compared to the commercial probe. There was a strong correlation between PPG amplitude and arterial pulse pressure. A further study comparing the results with arterial oxygen saturation would be needed in order to ascertain the true accuracy of the probe.

CHAPTER FIVE–PHOTOPLETHYSMOGRAPHIC SIGNALS OBTAINED FROM THE ABDOMINAL CAVITY

5.1 Introduction

In anaesthesia and critical care, there remains an area of unmet need– the ability to adequately and accurately measure splanchnic perfusion. In critical care and under anaesthesia, where mean arterial blood pressure and hence organ perfusion is lowered secondary to drugs given or primary pathology of the patient, the adequacy of perfusion of the gut and liver is likely of major importance in those that are critically ill. This is because inadequate perfusion could be associated with hepatic and gut injury and dysfunction and consequently increased patient morbidity and mortality.

The small intestine is the longest part of the alimentary tract and extends from the pylorus of the stomach to the ileocecal junction. It is divided into three parts: the duodenum, jejunum and ileum. The blood supply of the duodenum is from a branch of the gastroduodenal artery. The pancreaticodueodenal vein drains into the portal vein whilst the inferior vein joins the superior mesenteric vein. The lymphatic vessels follow the arteries and drain upward via pancreaticoduodenal nodes to the coeliac nodes and also down towards the superior mesenteric nodes. The jejunum and ileum receive their arterial blood supply from branches of the superior mesenteric artery. The intestinal branches arise from the left side of the artery and run in the mesentery to reach the gut. They form an anastomosis with one another, with the lowest part of the ileum supplied by the ileocolic artery. The veins of the jejunum and ileum correspond to the branches of the superior mesenteric artery and drain into the superior mesenteric vein. The lymphatic drainage is via the mesenteric nodes. (96)

The large intestine extends from the ileum to the anus with its primary function to absorb water and electrolytes and store undigested material till it is expelled as faeces. The blood supply of different parts of the gastrointestinal tract is related to the position in the abdominal cavity but is all essentially branches derived from the mesenteric arteries. One of the most important accessory organs of the gastrointestinal tract is the liver, which is also the largest known gland in the human

body. It has many functions including metabolism of fat, protein and carbohydrates; secretion of bile; filtration of bacteria and foreign particles in the bloodstream. It lies in contact with the abdominal part of the oesophagus, stomach, duodenum, right kidney and the gall bladder. It is tradition to divide the liver into the right and left lobes. The right and left branches of the hepatic artery and portal vein, right and left hepatic ducts are distributed to the right and left lobes of the liver respectively. The liver is completely surrounded by a fibrous capsule and is made up of liver lobules. The central vein of each lobule is a tributary of the hepatic veins. There are spaces between each lobule called the portal canals–within which lie branches of the hepatic artery, portal vein and a tributary of a bile duct, all collectively forming a portal triad. The arterial and venous blood passes between the liver cells by means of sinusoids and drains into the central vein. The hepatic artery, a branch of the coeliac artery, supplies the liver via its right and left terminal branches. The portal vein also divides into the left and right terminal branches behind the arteries and emerges from the posterior surface of the liver draining into the inferior vena cava. The blood vessels that bring blood to the liver are the hepatic artery and portal vein. The hepatic artery brings oxygenated blood to the liver while the portal vein brings venous blood rich in the products of digestion. The arterial and venous blood is conducted to the central vein of each liver lobule by the liver sinusoids, draining into the right and left hepatic veins. These leave the posterior surface of the liver and open directly into the inferior vena cava. Large amounts of lymph are also produced by the liver (about one-third to one-half of total body production), which then leave the liver and enter lymph nodes in the porta hepatis. (97)

There are several risk factors, which increase the likelihood of inadequate organ perfusion. Certain surgical procedures, such as cardio-pulmonary bypass surgery or abdominal aortic aneurysm surgery, peri-operative hypotensive episodes, the use of vasopressors either directly or indirectly affects the adequacy of end organ perfusion. Perfusion deficits remain a real risk with any form of prolonged hypotensive episodes, which can lead to organ ischaemia, infraction and death. Whilst there remains much controversy over the actual mechanisms where by some of the above procedures, such as cardio-pulmonary bypass surgery, have on affecting gastrointestinal function, there still remains no direct means of measuring the adequacy of end organ perfusion. In cardio-pulmonary bypass surgery, although the

incidence of gastrointestinal complications is relatively low (0.3% to 3%), they are associated with a high mortality rate (13% to 63%). It is widely accepted that global measurements of oxygen delivery, consumption and extraction do not provide reliable information on the adequacy of tissue oxygenation.

Gastric mucosal tonometry has been used for assessing splanchnic perfusion in various clinical settings. (98) This involves the indirect measurement of gastric mucosal pH and is a minimally invasive way of assessing the adequacy of tissue oxygenation. (98) Acid-base balance in tissue is determined primarily by the balance between the protons released during the release of energy by ATP hydrolysis and consumption by the resynthesis of ATP during oxidative phosphorylation. When the rate of oxygen delivery cannot meet the need for resynthesis of ATP in response to the energy requirements of the tissues, the rate of ATP hydrolysis exceeds the rate of synthesis and the pH decreases in proportion with the degree of unreversed ATP hydrolysis or dysoxia present. Thus, the measurement of gastric intramucosal pH gives a measure of tissue acid-base balance in a region of the body that is among the first to develop dysoxia in shock. The duration and degree of these episodes of dysoxia can be quite frequent and sustained in cases of shock in critically ill patients, despite the patients giving the appearance of being adequately resuscitated. During these episodes gastric mucosal acidosis are highly sensitive measures of the risk of developing “leaky gut “and its consequences, namely translocation, cytokine release, sepsis, multi-organ dysfunction and failure, and ultimately death. Gastric tonometry works by providing a tangible index of suspicion to clinicians of the adequacy of tissue oxygenation in one of the first parts of the body to exhibit dysoxia in shock. Measurement of gastric intramucosal pH is one way of being able to monitor and obtain readings that could provide an early warning system to the onset of tissue dysoxia and the opportunity to intervene early on to prevent further damage. Measurement of the regional gastric carbon dioxide tension as well as calculation of the difference between intramucosal and arterial carbon dioxide tension may give additional information about blood flow in the splanchnic area.

There are other blood tests or markers that, when used in combination with gastric tonometry, can give a rough indication of splanchnic function. Tests such as gamma glutamyl transpeptidase enzymes, which become elevated in liver disease, or

pancreatitis associated protein (PAP), which is a non-enzymatic secretory protein that becomes markedly elevated in the acute phase of pancreatitis. However these tests are unable to give an idea of splanchnic function or how well perfused the organs of the gastrointestinal tract are.

Whilst clinical biochemistry laboratory blood assays looking at body urea, creatinine, electrolytes, can give a rough non-specific estimation of how well the kidneys and liver may be functioning, it allows no indication of actual perfusion and viability of individual organs in the body. Conventional liver function tests such as serum albumin (Alb), alkaline phosphatase (ALP), alanine amino transaminase (ALT) and bilirubin can give an idea of how well the liver is functioning, and also an indication of the extent of any liver damage. However, an overall idea of perfusion of the organ cannot be ascertained just from liver function tests. Unfortunately, when blood test results become severely deranged, end organ damage is by then usually irreversible.

If one were able to continuously monitor splanchnic perfusion accurately, then any early tissue damage secondary to hypoxia could be picked up early and the appropriate treatment given prior to irreversible end organ damage. Whilst pulse oximetry has become a widely accepted method for monitoring arterial blood oxygen saturation, it has been tested experimentally to access intestinal oxygenation and hence viability in animal as well as human studies.(99) The preliminary results have shown to be promising with sensitive consistent readings given for detecting intestinal ischaemia. Currently, there are no commercially available pulse oximeter probes specifically designed for use to measure continuous oxygen saturation in the splanchnic region. This led to discussion into development of a probe capable of measuring oxygen saturation of the organs of the abdominal cavity, in a simple, quick fashion with minimal or no trauma to the patient. In the following study, a new avenue in fibreoptic technology will be explored to see whether a newly developed probe would be able to obtain adequate, clinically useful signals in terms of monitoring splanchnic perfusion in humans. The successful signal acquisition in the preceding studies provided the rationale to develop a probe, again based on fibreoptic technology, in a new study to see whether clinically meaningful PPG signals could be obtained from the external surface of abdominal organs during a laparotomy. (100)

5.2 Aims

The primary aim of this study was to see whether this newly developed probe could be used in the monitoring of arterial pulsation and oxygen saturation from the surface of abdominal organs. If successful, this would justify the development of a miniature monitoring probe for a larger evaluation study. The secondary aim of the study was to compare the PPG measurements obtained, from the probe which would be placed on various organs in the abdominal cavity, and to correlate this with finger pulse oximetry and ECG signals (see Appendix A).

5.3 Materials and methods

The fibreoptic probe was constructed with two fibreoptic leads. Like in the previous study, one cable was a receiving cable and the other a transmitting one. The fibres were connected to a processing system (electronic circuit board enclosed in a box) shown in figure 5.1. The circuit board comprised all optical components (light sources and photo detector) and electronic circuits used to drive the light sources and process the incoming signal from the tissues via the fibre. The processing system is battery operated (two 9V PP3 batteries). The abdominal pulse signals are sent to a computer. Software was written to display on the screen of the computer all of the signals acquired from the patient. The end of the probe was embedded in epoxy and inserted into a disposable sterile plastic sheath prior to it being used on a patient. Figures 5.2 and 5.3 show a photo of the probe close up from different views.

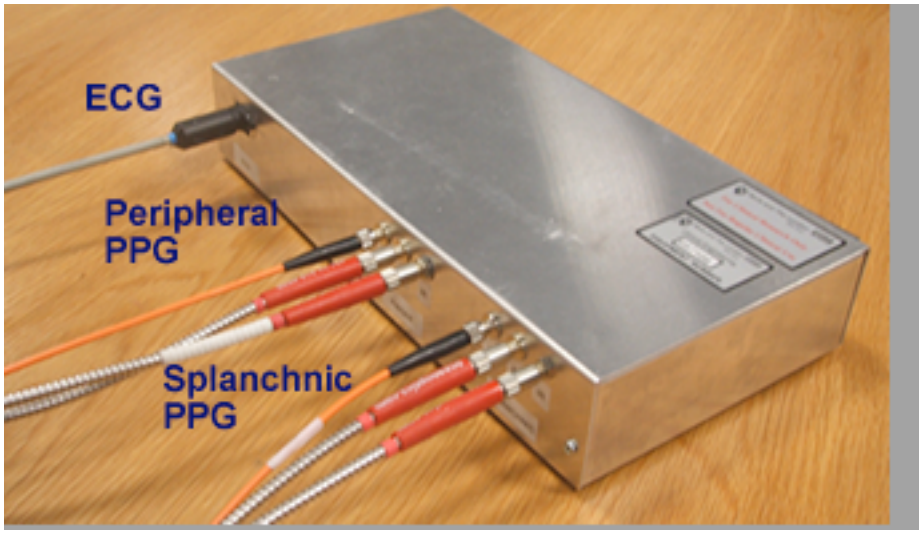


Figure 5.1 Photograph of the electronic circuit enclosed in a box.

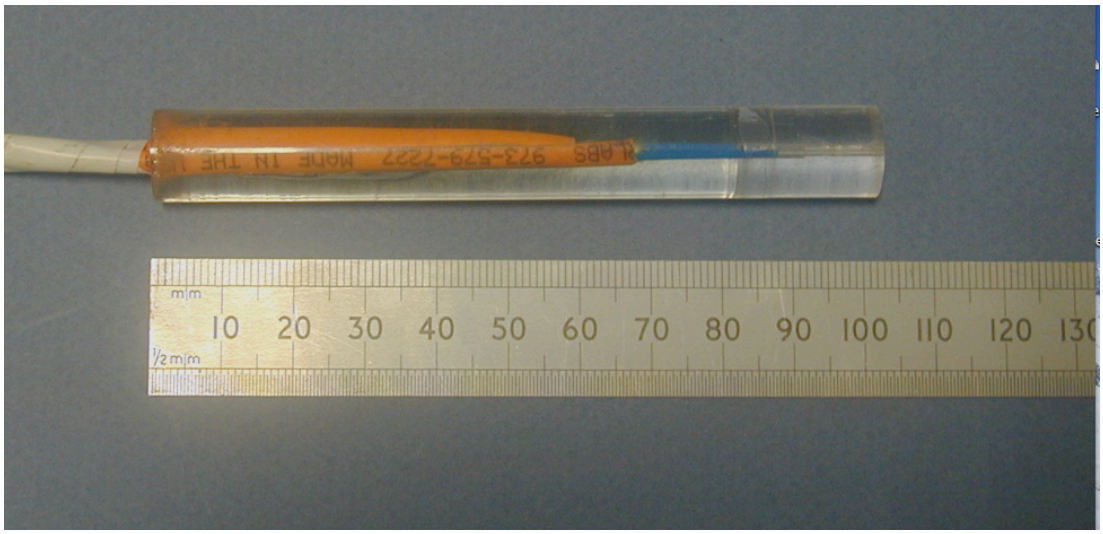


Figure 5.2 Photograph of the probe with a ruler for scale.

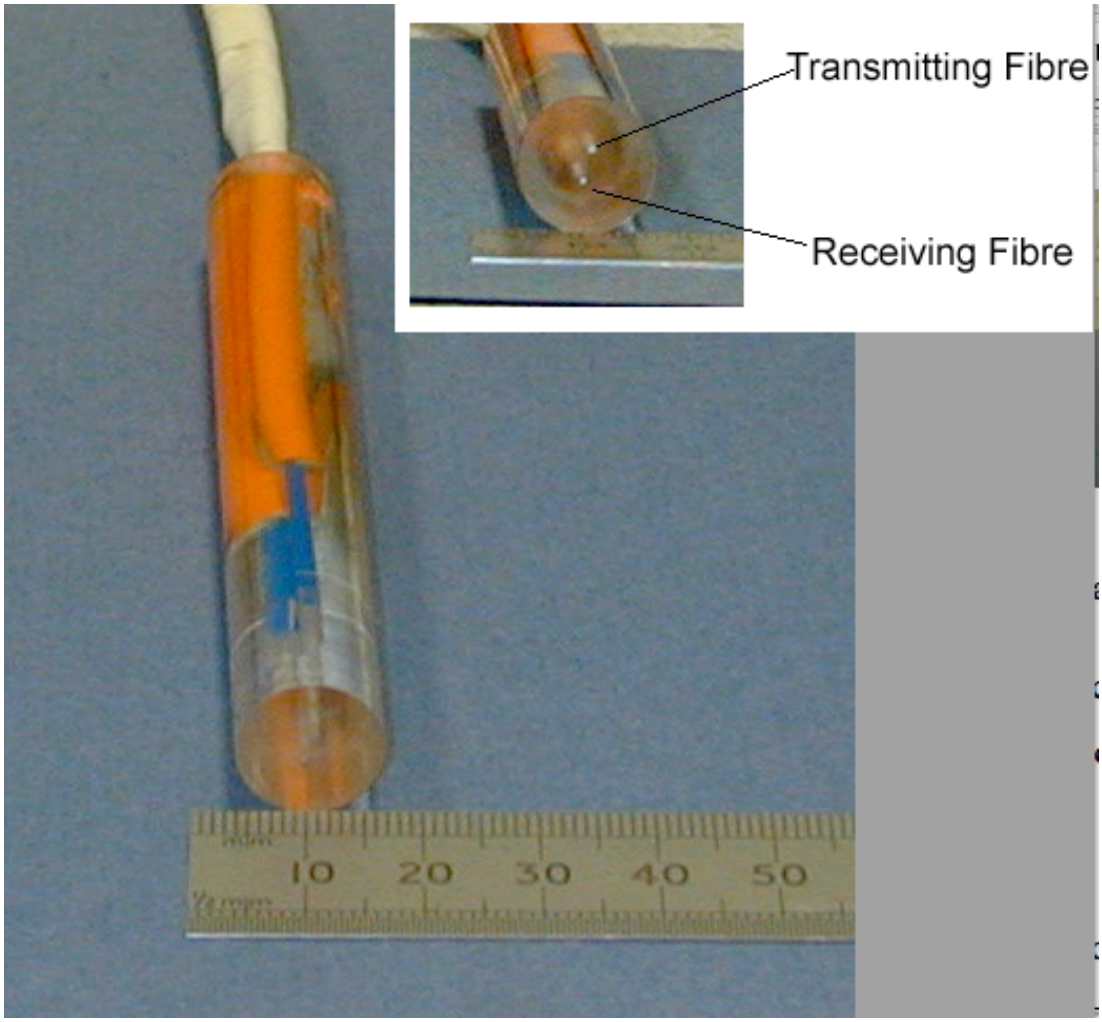


Figure 5.3 Photograph of the probe from the front showing the transmitting and receiving fibres.

A Lead II ECG channel was also included in the overall system to monitor the R waves on the ECG, which were used as a reference point for the splanchnic and finger PPG signals. Red and infrared PPG signals, red and infrared DC signals and ECG signals are digitised at a rate of 200 Hz by the National Instruments data acquisition card which was connected to a Toshiba laptop computer. These signals were then further processed using the LabVIEW system as in the previous studies. The acquired signals were filtered to remove any digitisation noise and displayed on the front panel of the virtual instrument. Finally, the signals were grouped together, converted into spreadsheet format and saved to a text file for post-analysis. Full ethics committee approval was obtained for this study. Patients suitable for recruitment into the study were those over the age of 18 years who were undergoing an elective laparotomy. Full informed consent was obtained from all patients. In

terms of data collection, all analogous data from the routine monitoring equipment was used i.e. ECG and finger pulse oximetry. Red and infrared PPG and DC signals from the surfaces of the organs, calculated arterial oxygen saturation from the organs and arterial oxygen saturation from a finger probe, as well as ECG was measured and recorded in a notebook computer. A block diagram of the system is shown below in Figure 5.4.

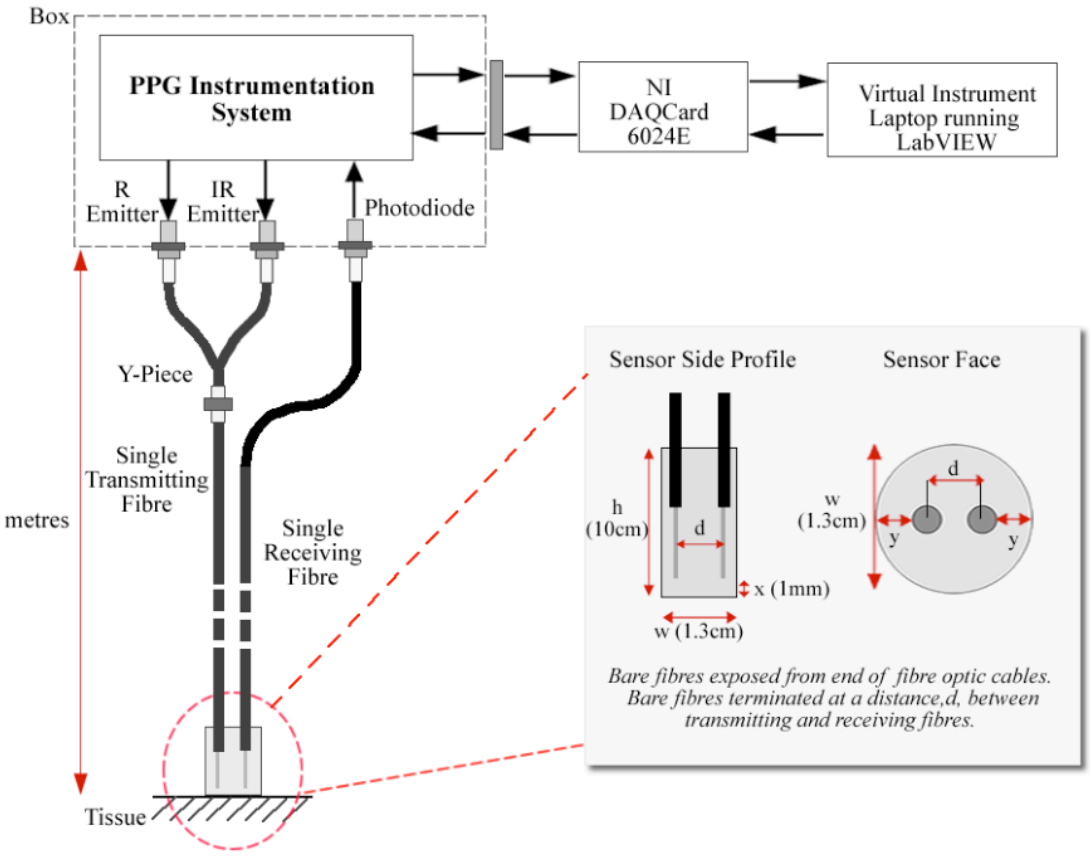


Figure 5.4 Block diagram of the PPG monitoring system adapted from (101)

In total 20 adult patients were recruited into the study, from elective operating lists within Barts Health NHS Trust. There were four male and sixteen female patients who underwent laparotomies for a mixture of general surgical, gynaecological-oncological and upper gastrointestinal surgical procedures.

After the induction of general anaesthesia, the patients were intubated and the lungs mechanically ventilated. Anaesthesia was maintained with inhalational isoflurane in a 1:2 mixture of oxygen and nitrous oxide. In addition to the standard monitoring employed for all patients undergoing general anaesthesia i.e. pulse oximeter, ECG,

and blood pressure monitoring, an additional set of ECG leads was attached for the purposes of the study. The fibreoptic peripheral PPG sensor was also placed on the finger of the patient. The fibreoptic splanchnic probe was sheathed by a sterile transparent cover and secured in place. At an appropriate time during the surgery, the fibreoptic probe was passed to the operating surgeon, and applied with minimal pressure, onto the surfaces of each available splanchnic organ, in such a way that the emitted light from the probe was reflected from the surfaces. During the measurement period, overhead operating lights were switched off to minimise any interference with the PPG sensor. During the measurement period, simultaneous AC and DC splanchnic PPGs as well as AC and DC peripheral PPGs and ECG signals were recorded for approximately two minutes at each different splanchnic site from which recordings were being taken. At the same time the PPG readings were taken, oxygen saturation readings from a peripheral commercial pulse oximeter as well as heart rate and non-invasive blood pressure readings were also recorded from the monitors in the operating theatres.

5.4 Results

In total 20 patients were recruited, but three patients were excluded from the final analysis, due to the peripheral fibreoptic probe becoming detached from the finger in one, and in the other two, the duration of the monitoring period was too short to acquire suitable signals for analysis. Patient demographics for all patients are shown below in table 5.1.

Male:Female	3:17
Mean age (±SD)	52.9 years (11.4)
Mean height (±SD)	165.9 cm (9.8)
Mean weight (±SD)	81.2 kg (16.5)
Mean BMI (±SD)	29.3 (5.0)

Table 5.1 Patient demographics

In total, 41 splanchnic sites were investigated: there were 17 measurements taken from small bowel, 14 from large bowel, five from the liver and five from the stomach. Good quality PPG signals were obtained from all the sites investigated. The

acquired traces were in sync with the obtained peripheral PPG signal as well as the ECG signal. This thus implied that the measured signal from the small bowel represents the movement of the cardiac pulse throughout the splanchnic tissue. There were some artefacts possibly from the lungs being ventilated mechanically or movement by the hand of the surgeon holding the probe, but this had no significant effect on the readings obtained. For each splanchnic sited that was used, mean AC and DC amplitudes were calculated for the red and infrared signals by averaging the PPG amplitudes over approximately two minutes of data recording. The corresponding mean AC and DC amplitudes for the red and infrared peripheral signals were also calculated.

A mean of the means splanchnic and AC and DC signals for each site were calculated for each of the four sites as well as the peripheral readings. In general the mean of the means AC amplitude from the large and small bowel were similar, these were smaller than the mean of the means AC amplitude obtained from the liver, but bigger than the mean of the means AC amplitude from the stomach and about four times bigger than that obtained from the peripheral PPG signals. There was good correlation of the mean of the means DC amplitudes from all four splanchnic sites – small bowel, large bowel, liver, stomach and the peripheral sites. However, the DC amplitudes were all approximately seven times larger than that obtained from the periphery. Figure 5.5 and Figure 5.6 show a sample PPG trace, displayed alongside the ECG trace, obtained from signals taken from the large and small bowel respectively. The traces represent good quality PPG signals.

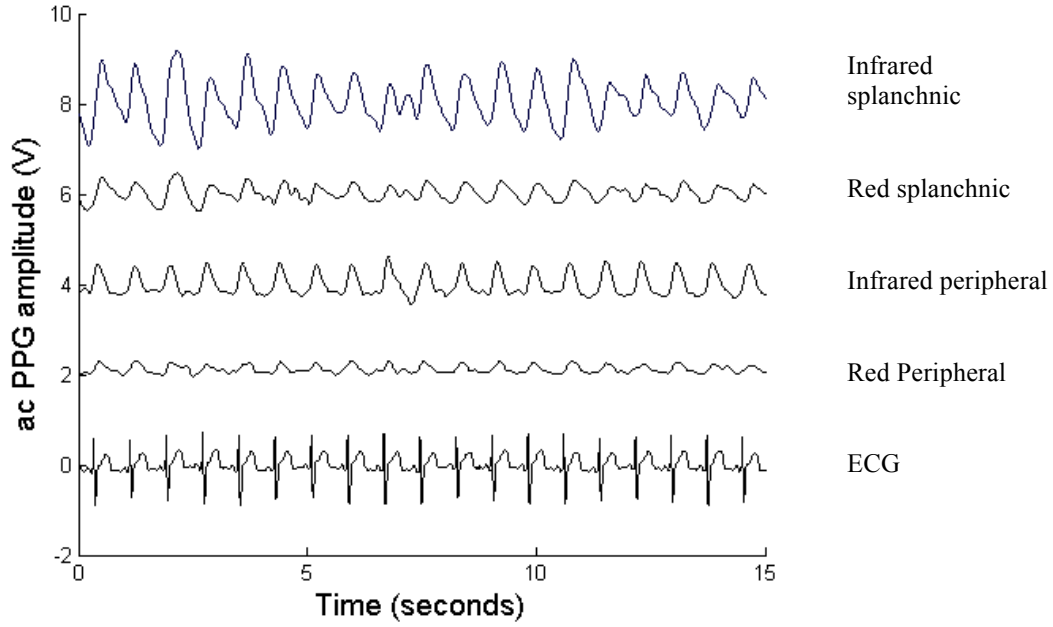


Figure 5.5 AC PPG signals from the large bowel. Adapted from (102).

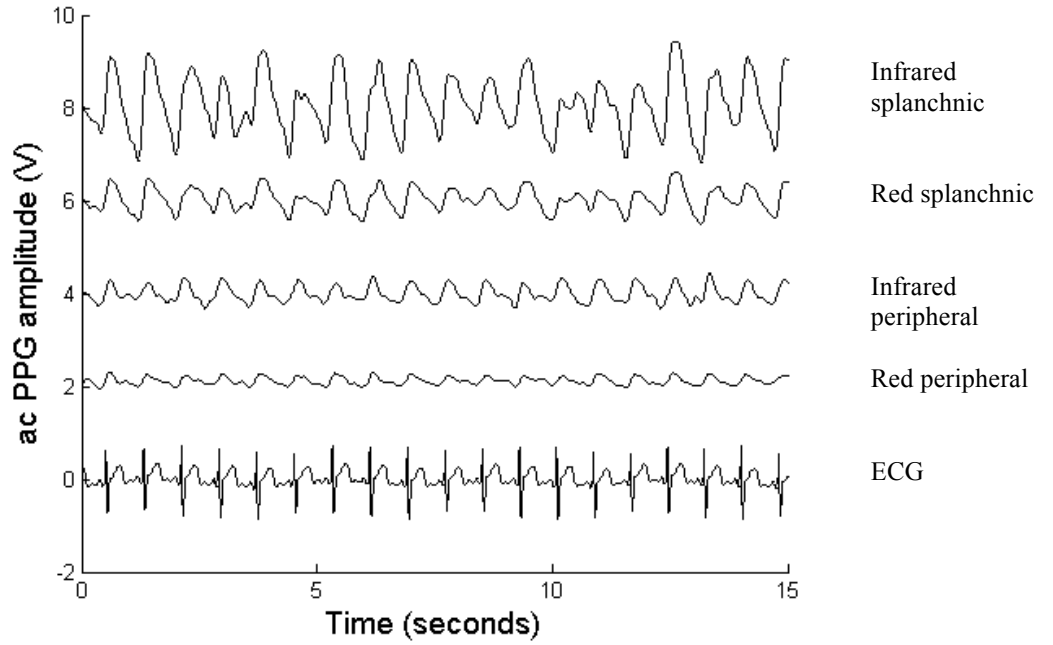


Figure 5.6 AC PPG signals from small bowel. Adapted from (103).

In order to access the ability to estimate oxygen saturation, bearing in mind that this was an uncalibrated system, preliminary SpO_2 values were estimated for each site under investigation, in order to see how feasible it would be to estimate blood oxygen saturation. For each two-minute period of monitoring, mean splanchnic and

peripheral SpO_2 values were estimated by obtaining an average of SpO_2 values over two minutes of data. The values obtained from the commercial pulse oximeter, over the two-minute period, were also averaged to obtain a mean value.

The mean of the means SpO_2 value obtained from the peripheral fibreoptic probe (97.94%) agreed well with the values obtained from the commercial pulse oximeter (97.88%). With respect to the SpO_2 values obtained from the large bowel (97.14%) and small bowel (97.41%), these were in good agreement with those obtained peripherally. The mean SpO_2 obtained from the stomach was 95.80%, and the mean SpO_2 obtained from the liver was 100.60%.

5.5 Discussion

From this pilot study, we managed to obtain good quality PPG signals from all the splanchnic sites under investigation. The estimation of SpO_2 involves calculating the amount of light transmitted through the tissues and hence despite the varying signals, SpO_2 can be calculated from these sites. There were a few artefacts attributable to either ventilator movements or to the personnel holding the probe, but overall, the signals showed good depth, strength and reliability. When looking at the mean of the means of both the AC and DC signals at the different sites the readings were taken from, there was found to be differences in amplitude. For example for the large bowel and small bowel there was found to be a significant difference between the signals obtained from these sites compared to those obtained from the periphery. The magnitude of these differences was more than three times larger than those obtained from the peripheral probe. This essential difference is not unexpected as there is a great difference in the vascular supply of both areas in question. The tissue overlying the peripheral skin consists of a thick epithelium on the outermost, superficial surface that contains no blood vessels.

In comparison, the surface lining the large and small intestines is a thin serosal mucosa, which has secretory functions and an underlying connective tissue layer. The mucosal epithelial lining is extremely thin and porous (less than 100 micrometres in thickness) and hence the distance of the blood vessels is much closer to where the probe would rest compared to when taking measurements from

the finger. There is also a greater volume of blood, pulsating throughout the splanchnic sites compared to at the finger and hence the expected larger signals obtained at those sites compared to the periphery. There is also less chance of any light being absorbed by the thicker epidermal tissue on the finger compared to in the large and small intestinal sites. Looking at the signals obtained from the stomach, these were smaller in amplitude compared to the other splanchnic sites, but still larger than those obtained from the peripheral probe. These results again suggest that the difference in tissue and vascular supply between the two sites account for the difference in amplitude of signals obtained.

Similarly for the liver, the difference in amplitude of the signals obtained were again much larger than that obtained from the periphery due to the vascular nature of the liver. It must be borne in mind the anatomy of the liver is different from the other organs as described in detail in the introduction to this chapter. The hepatic arteries supply arterial blood to the liver with oxygen being supplied from both the hepatic portal veins as well as the arteries. Blood flows through the sinusoids and drains into the central veins of each lobule. The central veins merge into the hepatic veins which exit the liver into the inferior vena cava.

However, it appeared likely, bearing in mind the small sample size of five patients, that there may be an underlying difference between the PPG signals obtained from the liver compared to the other splanchnic sites. However, there was also a difference in the SpO_2 values obtained from the liver compared to the commercial pulse oximeter. This could be due to the vascular nature of the blood supply to the liver. It has to be noted that the calculations were made with the small sample size of five patients. There were no complications associated with use of this probe in this patient group.

5.6 Conclusions

This was a pilot study to evaluate a newly developed fibreoptic probe designed for the purpose of obtaining signals to allow the calculation of arterial oxygen saturation. 20 patients in total were recruited for this study with the signals from 17 patients included in the final analysis. In all 17 patients, good quality signals were

obtained from all of them. PPG signals from splanchnic organs, peripheral PPGs as well as ECGs were noted for the monitoring period. Values from commercial pulse oximetry were noted during the monitoring period. In all cases, the preliminary SpO_2 values from each splanchnic site showed a good correlation with the values obtained from the peripheral fibreoptic probe as well as the commercial pulse oximeter. There was a big difference in PPG amplitudes obtained from the splanchnic sites compared to the corresponding peripheral sites in each of the subjects. This was likely due to the difference in vascular component of the splanchnic tissues compared to the peripheral tissues affecting transmission of light as well as amount of blood flow through the tissues. The estimation of SpO_2 from the splanchnic sites showed a good correlation with the values obtained both from the peripheral probe as well as the commercial pulse oximeter. (104) The sample size from the liver and stomach were too small to make more conclusive calculations. Further larger studies are needed in order to further evaluate the usefulness of this probe.

CHAPTER SIX–OVERALL SUMMARY AND CONCLUSIONS

The overall aim was the evaluation of innovative fibreoptic probes specifically constructed for the purposes of being able to measure PPG signals from different regions in the human body. These were used for the first time in the clinical population, and showed good quality viable signals yielding positive results. A total of 47 patients were recruited, of which 44 yielded good quality signals. The four that were excluded from subsequent signal processing and analysis were because of poor signal quality [n=1], or inadequate time to record [n=2], or the probe becoming detached from finger [n=1]. None of the patients suffered any untoward side effect attributable to the research studies.

The aim of my research was to clinically evaluate novel methods of measuring oxygen saturation in human tissues using photoplethysmographic fibreoptic technology. In conjunction with biomedical engineers at City University, innovative fibreoptic probes were designed and constructed with this in mind i.e. to measure oxygen saturation at various sites in the body. This is of relevance to particular clinical patient populations, in whom there is an unmet need in patient monitoring. A series of pilot studies were proposed and research ethics approval sought in order to carry out research on the patient population using the various probes.

Research ethics approval was successfully sought for all of the clinical studies with modified probes and materials used in each of them, along with MHRA approval as appropriate. These were innovative new probes designed specifically in each of the studies to be able to obtain the potentially useful signals needed for final analysis. These were all pilot studies done in carefully selected patient population groups.

The expected recruitment number in the studies of the oesophageal probe and the splanchnic probe were achieved [n=20] in each. For a pilot study, and with statistical advice, this was felt to be an adequate number in order to make the preliminary assessments on each of the probes. In the study evaluating the fibreoptic probe that was used to measure brain oxygen saturation in elective neurosurgical patients, a total of six patients were recruited. Whilst the initial target of ten patients for this

study was not met due to logistical reasons, the signals obtained from all six were of good quality and consistency to be able to make an informed assessment of the potential usefulness of the results obtained in that clinical group of patients. The implementation and results were entirely novel, in that this was the first time, that red and infrared PPG signals have been obtained directly from human tissue (brain) using fibreoptic technology. Technically these measurements validated the design, construction and materials used, in terms of fibre type, inter-fibre separation, LED drives current and depth of penetration. There were difficulties in assessing whether some of the results were due to arterial or venous pulsation in the brain, which could lead to potential difficulties in the future with accuracy or methodology of true arterial measurements.

With respect to the usefulness of the probe in the longer term on patients with brain pathology on the intensive care unit, only one patient had been recruited thus far. This one patient had suffered an intracerebral haematoma. It would have been good to have more patients with different brain pathologies in order to compare and contrast any results. Indeed, it would have been useful to have recruited a few trauma patients, with head injuries, in order to relate the PPG signals to ICP readings, that would have been obtained, and to the eventual outcome in such patients. It would have been ideal also to have been able to obtain signals over a more prolonged period of time i.e. to have kept the fibreoptic probe in situ in a patient with an intracranial bolt present and to see whether signals of good quality could be obtained over a prolonged period of time and whether it would have been feasible to have kept the probe in situ for a period of 48 hours. There were problems with the intracranial probe in terms of interference from movement artefacts – either due to external factors such as patient or staff movement or interference from diathermy in the operating room, the stealth machine and ventilatory artefacts. In terms of probe materials and construction, it was a robust model that was easy to use and handle. Due to the small sample size of the pilot study, the accuracy of readings obtained cannot be further commented on.

Nevertheless, the initial readings were promising and warrant further study to allow a more detailed analysis of the technique and to see if it can offer advantages over current monitoring technology. It would be interesting to see how future results

would compare with readings from jugular bulb oximetry, though this would give an indication of global oxygen saturation, rather than local oxygen saturation as measured by the fibreoptic probe. One potential source of error, was if a blood clot was surrounding the tip of the fibreoptic probe, this could lead potentially to over or more likely under readings of oxygen saturation. The initial successful signal acquisition using fibreoptic technology provided the justification for the development and clinical study of probes using this same technology platform, to measure PPG signals in the oesophagus and in the abdomen.

Firstly, the fibreoptic oesophageal probe was evaluated. A total of 20 patients were recruited of whom 19 yielded signals that were suitable for final analysis. The study was similar in design to that using a miniaturised oesophageal probe. This new probe had the advantage that no electrical components were placed internally in the patient. Good quality signals were obtained and the derived SpO_2 results were comparable with peripheral pulse oximetry readings. However, the gold standard of CO-oximetry was not available for use in this pilot study in order to make a better prediction of how accurate the correlation would be to arterial oxygen saturation. The probe is a robust model though it is prone to movement artefacts. The ease of use, in terms of insertion into the oesophagus was smooth and without any complications. In the anaesthetised patient, it could remain in situ for prolonged periods though this was not looked at in the study. One of the potential usefulness of such a probe, is of course for use in patients where peripheral pulse oximetry would be inaccurate or not possible for example in patients with hypothermia or burns. Further studies looking at its use in such a patient group, with comparisons to arterial oxygen saturations via CO-oximetry, would be needed in order to ascertain its accuracy in the measurement of oxygen saturation. Again, longer term monitoring periods, for example in the intensive care setting, would be useful in order to evaluate its use over a longer time period as well as to assess its robustness for use as part of additional monitoring in an intensive care setting.

The potential for use in continuously monitoring oxygen saturation in patients using the oesophagus as a site is enormous. The possible advantages it would have over the commercially available finger pulse oximetry is that of:

a) almost instantaneous readings with no lag time compared with a conventional pulse oximeter.
b) independent of peripheral perfusion or the assumption of viable digits to use as monitoring sites. For example in patients who have been affected by severe burns or have had limb amputations. Whilst the probe would be most comfortably tolerated in the sedated patient; newer, less invasive probes could be developed that rest in the upper airway that may be better tolerated. It has to be borne in mind that frequently, nasogastric tubes of the same size are put down the nose and into the oesophagus and hence stomach of awake patients, whilst in hospital for purposes such as feeding or gastric emptying.

In the last described study, an evaluation of a fibreoptic probe used to measure oxygen saturation in splanchnic organs was undertaken. A total of 20 patients were recruited to this study. 17 out of the 20 patients recruited had results that were suitably sufficient for analysis. The strength of this study was that the probe was constructed in such a way that it could be used interchangeably to measure PPG signals from any body cavity. It could be used in any open area in the abdomen that the operating surgeon has access to; all that was needed was a sterile plastic sheath in which to enclose the probe. There were good quality signals obtained from all the splanchnic sites under investigation. There was also a very good correlation with the readings taken from the peripheral commercial finger pulse oximeter. The signals obtained were again prone to interference from movement artefacts and would have very likely been affected by surgical diathermy as well if this had been on during the time of the recordings. In the clinical situation, if there were any clinical concerns about arterial oxygenation, and hence perfusion of vital organs, any monitoring period would have been absent from the effects of diathermy to allow the best possible readings to be taken. Whilst there was a close trend seen with the readings taken from standard pulse oximetry, there were no comparisons in this pilot study with measurements from arterial CO-oximetry.

The success of these pilot studies looking at the use of a fibreoptic probe to give almost instantaneous readings, which can be translated into clinically meaningful readings, will form the basis of more research into the area and further development of such probes on the medical engineering front. The scope for the use of fibreoptic

technology to measure oxygen saturation in tissues can be applied to most body cavities. The potential usefulness to be able to measure brain oxygen saturation, offering a novel tool for the monitoring of patients with brain pathology has the potential to contribute to the way we can monitor patients with head injuries. In addition, with further development, it is entirely feasible that other functions such as electrolytes, glucose measurements and so on could be achieved using this technology.

The development of a fibreoptic probe that could measure one and perhaps even more modalities in addition to oxygen saturation- such as carbon dioxide tension, glucose and other metabolites could have a significant impact on the way patients with brain pathology may be monitored in the years to come. It was shown that the fibreoptic probe could obtain good signals over a short period in a patient who had an ICP bolt in situ. The challenge would be in recruiting and evaluating how long the probe can remain in situ for, over a more extended period of time, in patients with brain pathology. Ideally, it should be able to remain in situ until the ICP bolt is no longer needed.

There is potential benefit for decision support and patient management that may be derived from being able to monitor oxygen saturation regionally and/or directly from tissues. Clinically meaningful signals, obtained from placing the probe on or in intra-abdominal organs such as the liver, stomach, large and small bowels, could have implications in clinical practice, if this is successfully validated in bigger studies. This could be a useful tool for the operating surgeon by indicating the perfusion of internal organs, which could be affected by surgical procedures such as bowel resections or reconstructive surgery.

Conclusions

These studies show that we can obtain good quality, viable PPG signals using fibreoptic technology. The studies also demonstrated that PPG signals could be obtained from numerous locations in the body and could have potential in the future for different monitoring modalities. For example, future developments would be to measure other variables such as arterial-venous oxygen differences in order to assess

oxygen uptake and utilisation. (104)(105)(106) Other uses could be in monitoring free-flap perfusion in reconstructive surgery. (107)

These were all pilot studies evaluating the use of specifically designed probes in the clinical setting. The number of patients targeted for each study was appropriate for a pilot project; however there were unforeseen constraints with recruitment of patients for the intracranial monitoring studies for different reasons. One was logistical in terms of availability of neurosurgical patients we could recruit from; the second, which contributed to a significant amount of research time being wasted was on getting agreement from the newly outsourced clinical sterilisation services to sterilise the fibreoptic probes for research purposes. The primary objectives in all the studies of obtaining good PPG signals and correlation with traditional pulse oximetry was successfully achieved. Ideally, comparison with blood co-oximetry would have been interesting but this would have required insertion of invasive arterial lines in all patients, most of whom would not have required one as part of their routine care. Some problems with obtaining measurements included movement artefacts, both from the surgeons as well as the operator holding the fibreoptic device. Interference from surgical diathermy, which is difficult to avoid in a theatre environment, was a significant problem, which needs to be taken into account when designing future probes. A filter to block the effects from diathermy would need to be incorporated.
There are limitations to any readings of oxygen saturation whether using conventional or more novel methods such as the ones described above. The advantage of using optical technology is the potential to monitor tissue oxygenation in regions of the body not accessed before by other methods, this could include not only arterial saturation, but venous saturation; any results should be looked at in conjunction with other methods, assimilating other parameters such as blood test results, metabolic states and overall well being of the patient. (108) These studies focussed on measurement of arterial oxygen saturation, which is of course distinct from ‘tissue oxygenation’. Note that tissue oxygenation can refer to the partial pressure of oxygen in the extracellular fluid as measured by a Clark electrode, or in the case of near infrared spectroscopy, can refer to the overall oxygen saturation of the blood in arteries, veins and capillaries (‘Tissue Oxygenation Index’) (109). Normal arterial oxygen saturation measured in a specific tissue may indicate the presence of adequate delivery of oxygenated blood, but does not reflect the actual

oxygen utilisation, or the balance between the oxygen supply and the metabolic demand. As such, the measurements documented in this research should be evaluated in combination with other measurements such as tissue oxygenation pO_2 and/or Tissue Oxygenation Index in a future investigation. Ultimately readings used in the clinical setting should be interpreted in the context of other measurements as well as patients' underlying conditions, in order to support decisions regarding clinical interventions. I believe that future direction with monitoring oxygenation in the clinical setting would have to involve an integration of these different techniques and modalities in looking at oxygen flux in the body, so as to give a balanced and accurate picture of the physiological status of the patient.

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APPENDIX A

A.1 Protocol for oxygen saturation measurements on ITU

Protocol

Evaluation of a new method of measuring cerebral oxygen saturation in ITU patients via a cranial bolt.

Version 2: 25th March 2007

Protocol Approval

Principal Investigator

Print Name: _____

Signed: _____

Date: _____

CONFIDENTIAL: Further dissemination of this protocol may only be made with the permission of the Principal Investigator.

1. Title

Evaluation of a new method of measuring cerebral oxygen saturation in ITU patients via a cranial bolt.

2. Investigators

2.1 Principal Investigator

Prof Richard M Langford,
Director, Anaesthetic Laboratory, St Bartholomew's Hospital (SBH).

2.2 Other Investigators

Mr Justin Phillips, Principal Technologist, Anaesthetic Laboratory, SBH.
Dr Serene Chang, Clinical Lecturer, Anaesthetic Laboratory, SBH.
Dr Kishore Maney, Research Fellow, Anaesthetic Laboratory, SBH.

3. Aim

To establish proof of concept of a technique to facilitate measurement of cerebral oxygen saturation in patients recovering from head injuries and neurosurgery in whom cranial bolts are indicated as part of their routine care.

The study will:

- Enable us to find out whether it is possible to measure pulsatile photoplethysmograph(PPG) signals and oxygen saturation (SpO_2) directly from the brain tissue.
- Compare SpO_2 readings from the brain with measurements from a near-infrared spectroscopy (NIRS) system, a finger pulse oximeter and the patient's blood gas analysis results,
- Attempt to correlate changes in the PPG signal strength and SaO_2 readings with measured changes in cerebral perfusion pressure (CPP).
- Determine whether the brain tissue SpO_2 is a reliable indicator of cerebral wellbeing.

4. Background and Introduction

In some high-risk patients (such as those recovering from severe head injury or neurosurgery) secondary brain damage, caused by neuronal ischaemia and/or hypoxia is a common and potentially preventable cause of mortality and residual disability [1]-[2]. Secondary brain injury is associated with inadequate cerebral perfusion caused by hypotension, raised intracranial pressure, cerebral vasospasm/loss of CBF autoregulation, and/or traumatic arterial/venous disruption [3].

Near Infrared Spectroscopy (NIRS) is currently used to monitor the adequacy of cerebral perfusion by estimating Hb saturation. The accuracy of NIRS is compromised by attenuation and modulation of light by superficial tissues (e.g. skull, scalp) [4]. As non-invasive solutions have not succeeded fully in measuring brain oxygen levels [5], our developments have focused on probes that are positioned on

or in the brain via a hollow bolt screwed into the skull. We have developed a system based on pulse oximeter technology whereby oxygen saturation is calculated by measuring the relative absorption of two wavelengths of light by haemoglobin in the cells. The contribution to the total absorption of light by the arterial blood component is calculated by detecting the pulsatile PPG signal for each of the two wavelengths.

Unlike current commercially available oximeters, which utilise external sensors, transmitting light through skin, bone and other tissue, the optical fibre system provides a means of directly accessing the cerebral tissue. The system meets the clinical need of rapid accurate regional measurement of brain oxygen content reducing the chance of secondary brain damage, or death to the patient. Our group already has considerable experience in developing and validating miniaturised oximetry devices [6]. A fibreoptic device is the next logical step in this research programme.

5. Patients

5.1 Recruiting

We aim to recruit patients for the study, who require cranial bolts as part of their routine neurosurgical/intensive care. These will be consenting competent pre-operative neurosurgery patients, and the unconscious head injured patients, for whom a relative's assent will be sought.

We aim to recruit up to 20 patients.

5.2 Inclusion Criteria

- Patients scheduled for neurosurgery who require monitoring via an intracranial bolt.
- Patients who having suffered head injury/medical conditions who require monitoring via an intracranial bolt.

5.3 Exclusion Criteria

- Patients in whom more extensive intracranial monitoring is required (e.g brain tissue oxygen partial pressure and/or brain temperature monitoring). In these cases, two or three lumens of the cranial bolt will be required so the lumens will not be free for the optical probe.
- Patients who decline consent.
- Relatives of patients who decline assent.

6. Materials and Methods

6.1 Instrumentation

The probe is based on a pair of optical fibres and is designed to utilise two of the three channels of the LiCox IM3 Cranial Access System. This system is already routinely used for monitoring intracranial pressure and other parameters in post-operative neurosurgical patients and patients suffering from head injuries. The fibres are approved for medical use, are of biocompatible materials and will be supplied sterile.

The fibres will be connected to a box containing two (red and infrared) light sources, a photodetector, power supplies (two 12 V lead acid batteries), a circuit board and a computer interface. A block diagram of the system is shown in Figure 1. The circuit board performs the following functions:

- switching the light sources on and off
- amplification of the detected light intensity signals
- filtering the signals to remove interference
- separation of pulsatile (ac) signals from non-pulsatile (dc) signals
- synchronisation of computer data acqusition with light source timing.

The instrument box is connected to an analogue-to-digital converter (National Instruments Inc., Austin, TX, USA) installed in the PCMCIA slot of a notebook computer.

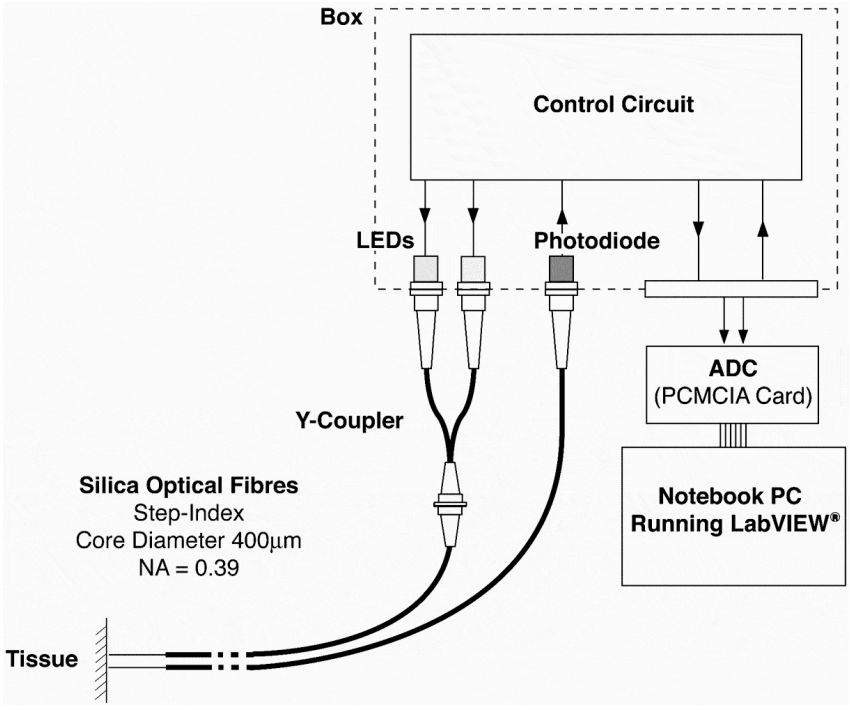

Figure 1: Block diagram of the PPG measurement system

6.2 Method

The clinical investigator will identify neurosurgical patients admitted to The Royal London Hospital for intensive care management of head injury, who require a cranial LiCox bolt and also pre-operative neurosurgical patients who require a cranial LiCox bolt. The emergency admission patients on the intensive care unit will be unconscious, and hence the investigator will approach the patient's relative for written assent. The pre-operative patients able to give informed consent will be approached by the investigator for written consent.

Patients in the ITU who have been recruited for the study will have bolts already inserted as part of their neurosurgical management. A clinician will insert the optical fibres into the bolt under sterile conditions. The fibres will be advanced until a good signal is obtained or any unexpected resistance is encountered. The fibres will penetrate 1-2cm into the brain tissue, as in the case with existing devices used with the LiCox bolts.

The placing of the optical fibre probe will be abandoned if there is any difficulty inserting the optical fibres into the cranial bolt or if requested to desist by any of the responsible clinical staff: the ITU clinicians, nurses or neurosurgeon/neurologist in charge of the patient's care. The fibres are locked with a self-sealing cap to prevent contamination and infection. At the beginning of the measurement period, a pair of NIRS probes will be placed on the forehead. Measurements will be recorded from the optical fibre system, the NIRS system and routine monitoring until the fibres are removed en bloc with the cranial bolt.

6.3 Measurements

Red and Infrared PPG and dc signals, calculated cerebral arterial oxygen saturation, calculated cerebral tissue oxygen saturation**,** cerebral oxygen saturation from an NIRS system, arterial oxygen saturation from a finger probe, intracranial pressure (ICP) and arterial blood pressure and derived cerebral perfusion pressure will be recorded.

7. Conduct and Monitoring

The study will be conducted according to ICH/GCP standards. The prinicipal investigator and members of the study research group will be responsible for monitoring the conduct of the study. The sponsor, Queen Mary University of London, may audit the study.

8. Data Analysis

The quality of acquired signals will be evaluated. The data will be stored on a password protected computer in a locked office up to a maximum period of 15 years. Only members of the research group will have access to the data. The analysis of data will take place at the Anaesthetic Laboratory, St Bartholomew's Hospital.

As this is a proof of concept study, the aim is to establish that reliable signals can be obtained using the fibre optic oximetry probe. At this stage in the development of the device, the present study is not intended to demonstrate the potential for medical

decision support. We are however planning to obtain preliminary comparative data in a pilot to justify a larger clinical evaluation study.

9. Reports of Study Results and Publication

It is intended to present the results of the study at a scientific meeting and publish in a peer-reviewed journal.

10. References

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A.2 Protocol for oxygen saturation measurements in the oesophagus

Protocol

Evaluation of a new method of measuring oesophageal oxygen saturation in anaesthetised patients using a fibreoptic probe

Version 3: 15-05-07

Protocol Approval

Principal Investigator

Print Name: Richard M Langford

Signed: _____

Date : _____

1. Title

A new method for measuring oesophageal oxygen saturation in anaesthetised patients

2. Investigators

2.1 Principal Investigator
Professor Richard M Langford
Director Anaesthetic Laboratory, St Bartholomew's Hospital (SBH).

2.2 Other Investigators
Mr Justin Phillips, Principal Technologist, Anaesthetic Laboratory, SBH.
Dr Serene Chang, Clinical Lecturer, Anaesthetic Laboratory, SBH.
Dr Kishore Maney, Research Fellow, SBH
Dr Panicos Kyriacou, Honorary Research Fellow, SBH.

3. Aim

To evaluate whether a newly developed oesophageal pulse oximeter probe based on optical fibre technology can provide meaningful and reliable signals from which useful patient monitoring measurements can be derived.

4. Background and Introduction

Pulse oximetry is widely used in anaesthesia and intensive care monitoring. It is a valuable, non-invasive optical monitoring technique used for continuous measurement of arterial blood oxygen saturation (SpO_2). In the late 1980s, pulse oximetry became the mandated standard for monitoring during anaesthesia. Although pulse oximeters generally give reliable readings of blood oxygen saturation, there are significant limitations on the accuracy and availability of pulse oximeter data in some circumstances. When peripheral perfusion is poor, as in states of hypovolaemia, hypothermia, vasoconstriction, low cardiac output and low mean arterial pressure, oxygenation readings become extremely unreliable or cease. To overcome the limitations of current commercial pulse oximeters where peripheral perfusion is compromised, we have developed miniaturised sensors that allowed the monitoring of SpO_2 values at more central parts of the body such as the oesophagus, on the hypothesis that adequate perfusion at these sites will be preserved, compared with the periphery [1]-[2]. Our studies have shown that measurable photoplethysmographic (PPG) signals and SpO_2 values can be detected in the oesophagus of healthy patients during anaesthesia and from patients undergoing cardiothoracic surgery [3]. The PPG signal is a potentially valuable indicator of both oesophageal perfusion and also general well-being. Following our experience in developing and validating miniaturised SpO_2 devices, the next logical step is the development of a fibreoptic device. The probe would be smaller, completely biocompatible and sterilisable and confer the added safety benefit of complete electrical isolation.

This proof-of-concept study will enable us to:
1) measure oesophageal oxygen saturation (SpO_2).
2) compare this with simultaneous readings from a finger pulse oximeter.

5. Patients

5.1 Recruiting

The patients will be recruited with their full consent as early as possible. This will be done either in the pre-operative assessment clinics or when they arrive in hospital the day before or early in the morning of their scheduled surgery.

5.2 Inclusion criteria

Adult patients aged (18-70) from whom full written informed consent will be sought.
Patients undergoing routine surgery who require a general anaesthetic including tracheal intubation as part of their anaesthetic.
Patients who fall into the American Society of Anesthesiologists scoring system of ASA I-III.
Patients with no known clotting abnormalities.
Patients who have no upper airway problems, or anticipated difficulty with intubation.
Patients with have not had previous major head and neck surgery.
Patients without a anatomical abnormalities of the upper airways or upper gastro-oesophageal tract.
Patients without a history of gastro-oesophageal reflux disease, hiatus hernia or previous oesophageal surgery.

5.3 Exclusion criteria

Patients who decline consent.
Patients with a known clotting abnormality.
Patients with an abnormal anatomy of the upper airways or upper gastrointestinal tract.
Patients with a history of gastro-oesophageal reflux disease or a hiatus hernia.
Patients with a history of oesophageal varices.
Patients with known oesophageal pathology or previous surgery to the oesophagus or stomach.
Patients who are an anticipated difficult intubation.
Pregnant women.

6. Materials and Methods

6.1 Instrumentation

An oesophageal probe has been developed which comprises a cylindrical epoxy moulding in which two optical fibres are embedded as shown in Figure 1. The probe will be inserted into a clean, sealed naso-gastric tube prior to insertion. The fibres are approved for medical use and are constructed from biocompatible materials.

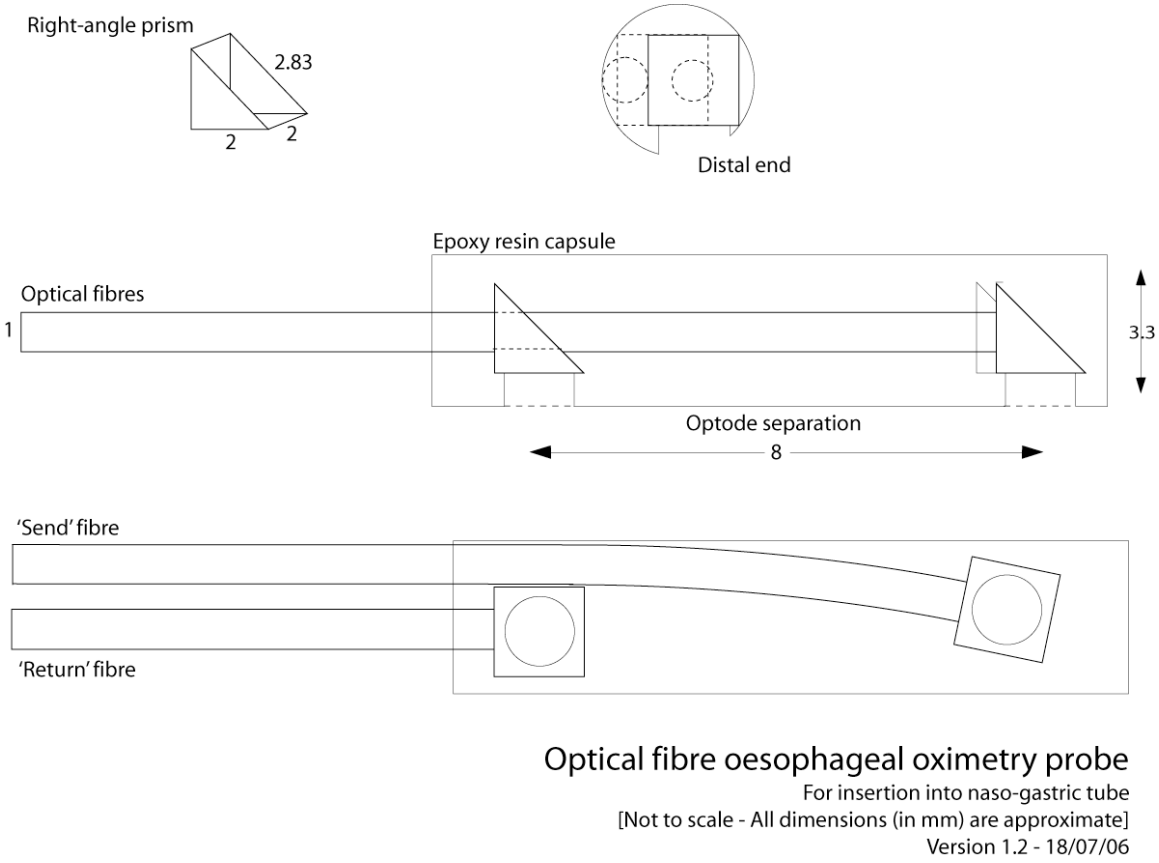

Figure 1: Oesophageal oximetry probe

The proximal end of the fibres will be connected to a box containing two (red and infrared) light sources, a photodetector, power supplies (two 12 V lead acid batteries), a circuit board and a computer interface. A block diagram of the system is shown in Figure 2. The circuit board performs the following functions:

- switching the light sources on and off
- amplification of the detected light intensity signals
- filtering the signals to remove interference
- separation of pulsatile (ac) signals from non-pulsatile (dc) signals
- synchronisation of computer data acquisition with light source timing.

The instrument box is connected to a data acquisition card (National Instruments Inc., Austin, TX, USA) installed in the PCMCIA slot of a notebook computer.

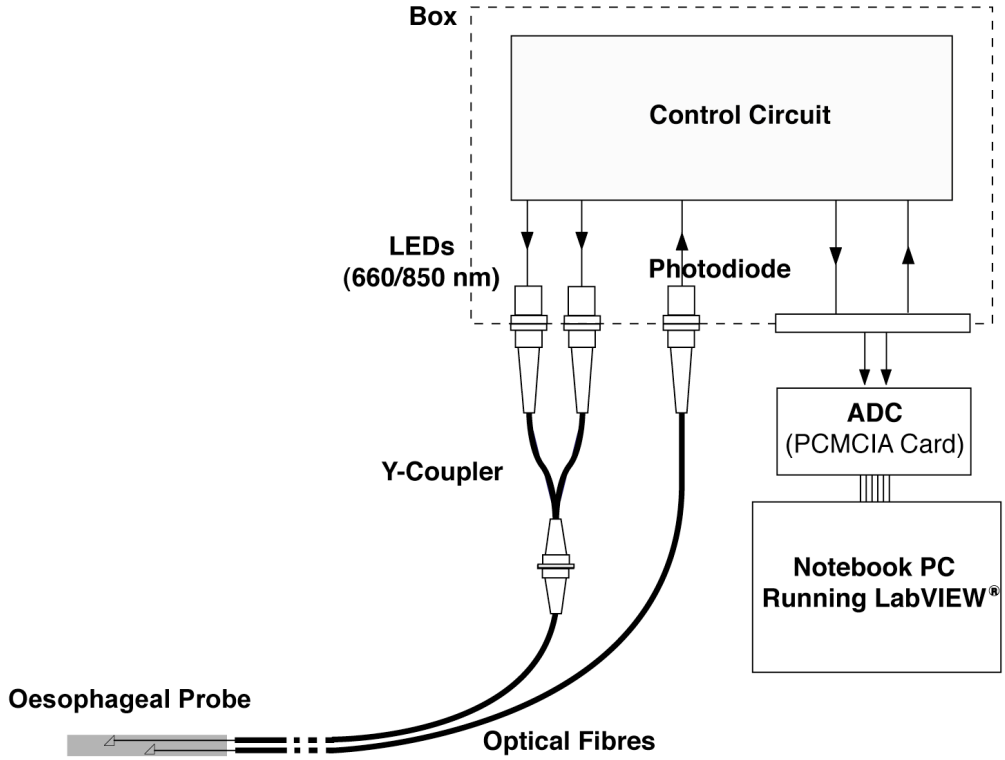

Figure 2 : Block diagram of the PPG measurement system

6.2 Method

The investigators will seek full written informed consent from the appropriate patients as early as possible before their scheduled surgery. A written information sheet will be provided. The surgeons, anaesthetists and theatre staff involved in the care of the patient will also be informed of the study and patients will only be recruited with their agreement to proceed with the study. We aim to recruit up to 20 patients.

Adult patients aged (18-70) and deemed 'low risk' by the American Society of Anesthesiologists score of (I-III) will be identified from the elective operating lists at Barts and The London NHS trust. Any patients in whom difficulty or increased risk of probe placement is anticipated, as listed by our exclusion criteria, will be excluded. Similarly, the research procedure will be abandoned if there is any difficulty with the anaesthesia or visualisation of the gullet or resistance to passage of the probe.
After induction of anaesthesia and immediately after tracheal intubation, the probe will be inserted into the gullet by the anaesthetist, via the patient's mouth, under direct vision with a laryngoscope and Magill's forceps so the tip is at a distance of 35 cm measured from the teeth. Once the probe is in position, the light sources will be switched on and signals recorded for one minute. The probe will then be withdrawn 5 cm at a time and signals recorded at each position until the probe is at a depth of 15 cm. The arterial oxygen saturation will be calculated continuously from the measured signals and recorded. This will be compared to peripheral pulse oximeter readings. The probe will then be advanced to the position which yielded signals of greatest amplitude and left in place while the surgery commences, during which time signals will be recorded continuously on the notebook computer. The arterial oxygen saturation will be calculated continuously from the measured signals and recorded. This will be compared to peripheral pulse oximeter readings. The probe will be left

in position for a total period of not less than 10 minutes and not exceeding 60 minutes. The probe will be removed at the end of the measurement period, before the patient is woken up. We plan to review each patient post-operatively, and will take this opportunity to both thank the patient for their participation and let them know if we were successful in obtaining potentially useful pulse wave signals.

6.3 Measurements

Red and infrared PPG and dc signals from the oesophagus, calculated arterial oxygen saturation and arterial oxygen saturation from a finger probe will be measured.

7. Conduct and Monitoring

The Chief Investigator and members of the research group will be responsible for monitoring the conduct of the study. The sponsor, Barts and The London NHS Trust, may audit the study.

8. Data Analysis

All data will be stored in a password protected computer in a locked office. All study data will be stored in a custom made password protected database which identifies the patient only by initials and a study number. Only members from the research group will have access to and perform the data analysis. This will take place at the Anaesthetic Laboratory, St Bartholomew's Hospital. Data will be stored for a maximum of 15 years and will be subject to internal review.

The quality of acquired signals will be evaluated. As this is a proof of concept study, the aim is to establish that reliable signals can be obtained using the fibreoptic oximetry probe. At this stage in the development of the device, the present study is not intended to demonstrate the potential for medical decision support. We are however planning to obtain preliminary comparative data in a pilot to justify a larger clinical evaluation study.

9. Reports of Study Results and Publication

The results of the study will be evaluated and publication of the results in a peer-reviewed journal is planned.

References

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A.3 Protocol for oxygen saturation measurements in the abdominal cavity

Protocol

Title:
Evaluation of a new method of measuring arterial pulsation and oxygen saturation from the surface of abdominal visceral organs using a fibreoptic probe

Version: 2
Dated: 12th December 2006

Protocol Approval

Principal Investigator: Prof Richard M Langford

Signed: _____

Date: _____

CONFIDENTIAL: Further dissemination of this protocol may only be made with the permission of the Principal Investigator

1. Title: Evaluation of a new method of measuring arterial pulsation and oxygen saturation from surfaces of abdominal organs during laparotomy.

2. Investigators:

2.1 Principal Investigator

Professor Richard M Langford
Director Anaesthetic Laboratory, Barts and the London NHS Trust (BLT)

2.2 Other Investigators

Dr Kishore Maney, Research Fellow, BLT.
Dr Serene Chang, Clinical Lecturer, Anaesthetic Laboratory, BLT.
Ms Michelle Hickey, Honorary Research Fellow, BLT
Dr Panicos Kyriacou, Honorary Research Fellow, BLT.
Mr Justin Phillips, Principal Technologist, Anaesthetic Laboratory, BLT.

3. Aim

3.1 Primary Aim:

Proof of concept study to evaluate a newly developed fibreoptic pulse oximeter probe used to monitoring arterial pulsation and oxygen saturation from the abdominal visceral organs surfaces.

It is hoped that this can provide meaningful and reliable signals, which could provide the basis for development of a miniature monitoring probe for a larger evaluation study.

3.2 Secondary Aims

To compare the measurements photoplethysmographic(PPG) signals derived from the new pulse oximeter probe placed on various sites on the abdominal organs with the PPG signals acquired from the finger probe.

We will try to correlate PPG signals with ECG signals.

4.Background and Introduction

Pulse oximetry is widely used in anaesthesia and intensive care monitoring. It is a valuable, non-invasive optical monitoring technique used for continuous measurement of arterial blood oxygen saturation (SpO2). In the late 1980s, pulse oximetry became the mandated standard for monitoring during anaesthesia.

Our previous studies have shown that measurable photoplethysmographic (PPG) signals and SpO2 values can be detected in the oesophagus of healthy patients during anaesthesia and in intensive care following cardiothoracic surgery [1,4,5]. Hence, an

intra-abdominal monitoring probe may prove to be a simple and potentially valuable continuous indicator of abdominal organ perfusion.

The study will enable us to:

1. Measure oxygen saturation (SpO2) of the abdominal organs.
2. Compare the measured oxygen saturation from the surface of abdominal organs with a finger probe (using the same fibreoptic technology) and commercially available finger pulse oximeter probes.

5. Patients

5.1 Recruiting

This is a proof of concept study and will be observational in design. The study will be conducted according to ICH/GCP standards. The patients will be recruited with their full consent as early as possible. This will be done either in pre-operative assessment clinics or when they arrive into hospital the day before their scheduled surgery.

5.2 Inclusion criteria

A. Adult patients undergoing elective laparotomy.
B. Adult patients from whom full written informed consent will be sought.

5.3 Exclusion criteria

A. Patients who decline consent.
B. Patients undergoing emergency surgery.

6. Materials and Methods

6.1 Instrumentation

A fibreoptic sensor for measuring oxygen levels in arterial blood in various abdominal organs (gut, liver, kidney) has been constructed. The probe consists of two fibreoptic leads. One is used to shine light at the tissue of interest and the other to bring any light back that is reflected from the surface of the abdominal organs. The fibres are connected to a processing system (electronic circuit board enclosed in a box). The circuit board comprises all optical components (light sources and photo detector) and electronic circuits used to drive the light sources and process the incoming signal from the tissue via a fibre. The processing system is battery operated (two 9V PP3 batteries). The abdominal pulse signals are sent to a computer. Software was written to display on the screen of the computer all the signals coming from the patient. A simple block diagram of the system is shown in Figure 1.The end of the probe is embedded in epoxy and it looks like a pencil type probe. Such geometry will allow the medical investigator or surgeon to have a good handle of the probe. Also the probe is inserted into a sterile plastic sleeve before use to make measurements on a patient.
An identical probe, like the one described above has been developed to measure the oxygen level in blood at the finger (Figure 2). The reason for two identical probes measuring oxygen levels in blood at two different locations is for comparison purposes.

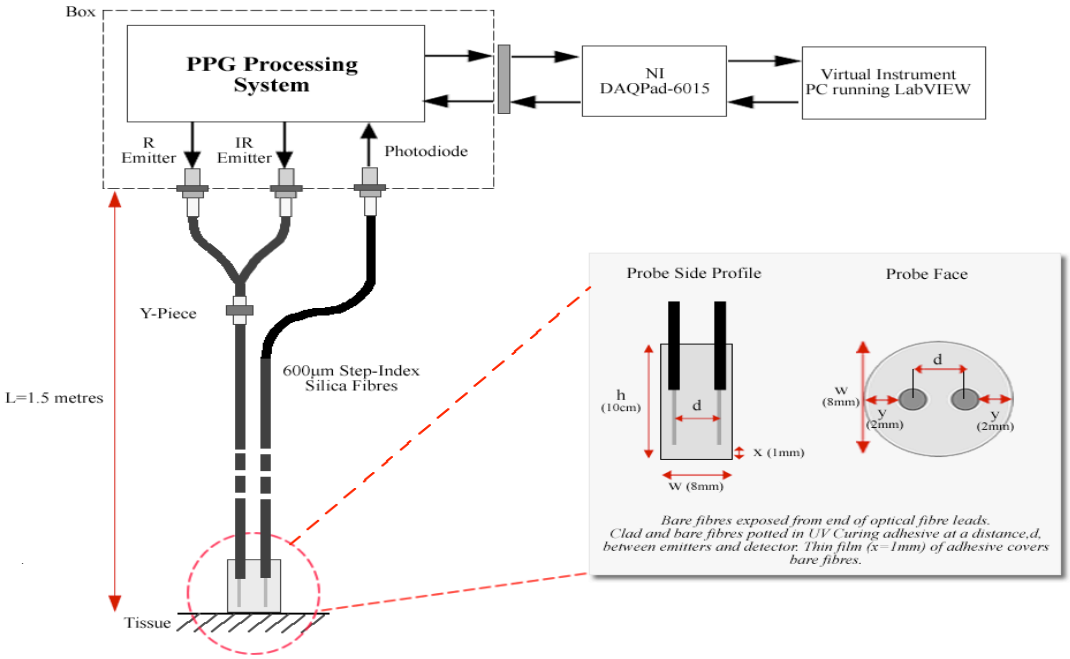

Figure 1

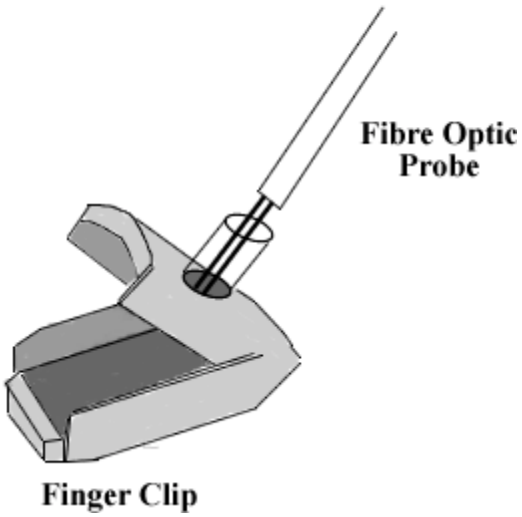

Figure 2

A Lead II ECG channel is also included in the overall system to monitor the R waves, which are used as a timing reference for the splanchnic and finger PPG signals.

Red and infrared PPG signals, red and infrared DC signals and ECG signals are digitised at a rate of 200Hz by the National Instruments data acquisition card which is connected to a Toshiba laptop computer. These signals are then further processed using LabVIEW. LabVIEW (Laboratory Virtual Instrument Engineering Workbench) is a programme development environment that utilises a graphical programming language, G, to create programmes in block diagram form. It relies on graphical symbols, rather than textual language (C, C++, Java) to describe programming actions. It is especially suitable for instrument control, data acquisition, and pre/post processing of acquired data. LabVIEW programmes are called Virtual Instruments (VIs) because their appearance and operation imitate actual instruments (see Figure 3).

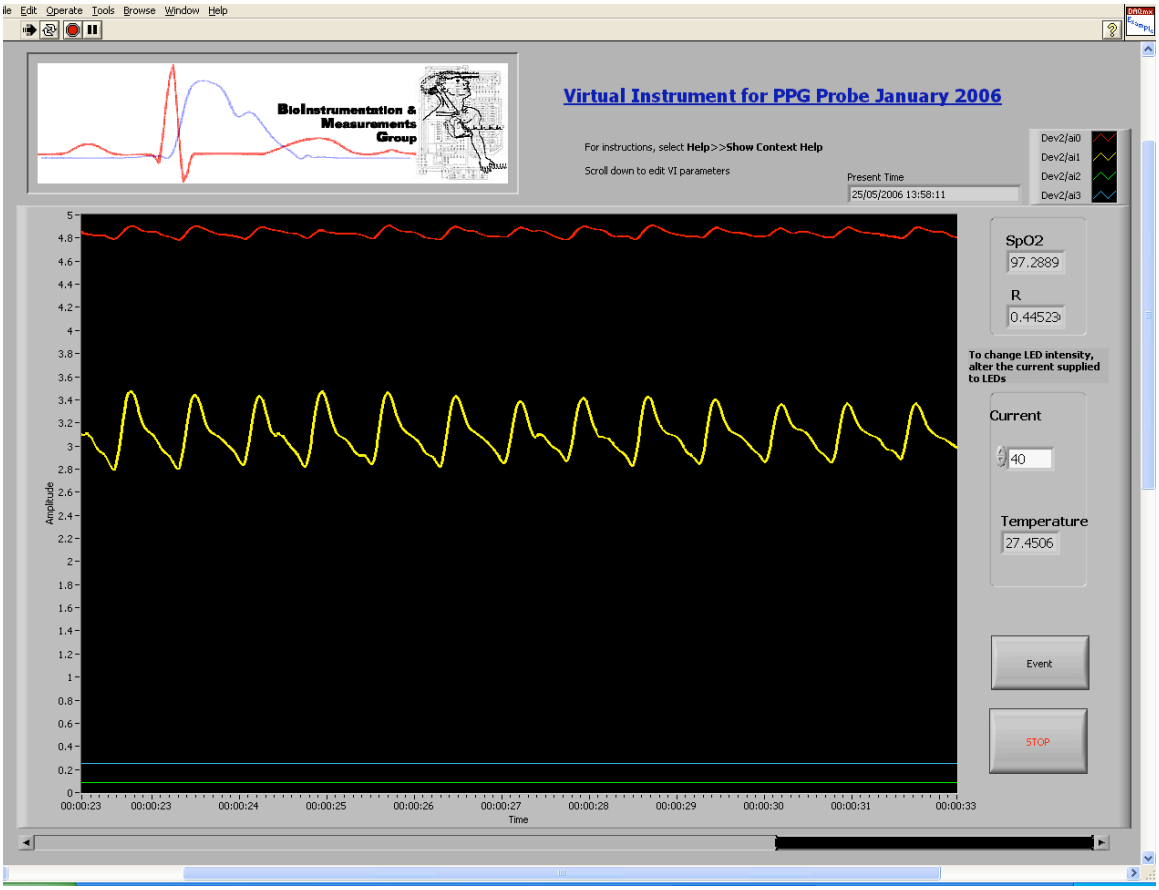

Figure 3 Front panel of virtual instrument showing the display.

The acquired signals are filtered to remove any digitisation noise and displayed on the front panel of the virtual instrument (See Figure 3). Finally, the signals are grouped together, converted into spreadsheet format and saved to a text file for post-analysis.

To minimise the risk to the patient from the electrical hazard associated with the accidental or unintended mains power up of the laptop computer, electrical isolation techniques were incorporated into the processing system.

6.2 Method

Adult patients who are about to undergo elective abdominal (laparotomy) surgery will be identified from the elective operating lists at Barts and The London NHS trust. The investigators will seek full written informed consent from the appropriate patients as early as possible before their scheduled surgery. A written information sheet will be provided. The surgeons, anaesthetists and theatre staff involved in the care of the patient will be informed of the study and patients will only be recruited with their agreement to proceed with the study. We aim to recruit up to 20 patients.

We intend to record all analogous data output from the routine monitoring equipment used intra-operatively in theatres by interfacing the monitors into the notebook computer if possible. If this is not possible then the ECG is recorded using additional set of ECG leads and recorder and a separate finger pulse oximeter which could be easily synchronised with PPG signals in the notebook computer.

6.3 Measurements

Red and infrared PPG and dc signals from the surfaces of the organs, calculated arterial oxygen saturation from the organs and arterial oxygen saturation from a finger probe, as well as ECG will be measured and recorded in a notebook computer.

7. Conduct and Monitoring

The principal investigator and members of the research group will be responsible for monitoring the conduct of the study. The sponsor, Barts and The London NHS Trust, may audit the study.

8. Data Analysis

All data will be stored in a password protected computer in a locked office. All study data will be stored in a custom made password protected database which identifies the patient only by a study number. Only members from the research group will have access to and perform the data analysis. This will take place at the Anaesthetic Laboratory, St Bartholomew's Hospital. Data will be stored for a maximum of 15 years and will be subject to internal review.

The quality of acquired signals will be evaluated. As this is a proof of concept study, the aim is to establish that reliable signals can be obtained using the probe. At this stage in the development of the device, the present study is not intended to demonstrate the potential for medical decision support. We are however planning to obtain preliminary comparative data in a pilot to justify a larger clinical evaluation study.

9. Reports of Study Results and Publication

The results of the study will be evaluated and publication of the results in a peer-reviewed journal is planned.

10. References

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